EXPLORING THE INFLUENCE OF DIET QUALITY ON VISCERAL ADIPOSITY AND RISK OF MORTALITY FROM NON-COMMUNICABLE DISEASES AMONG ADULTS IN THE US

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DEDICATION

I am dedicating this dissertation to my fiancé Matt, my parents, Naomi and Stephen, and my siblings, El'ise, Jessica, and Jorden, for their unconditional love and support.

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ABSTRACT

High visceral adipose tissue (VAT), more so than subcutaneous adipose tissue, is associated with an increased risk of chronic disease and mortality. Following a higher quality diet is associated with lower VAT, and a reduced risk of death from all-causes, CVD, and cancer. This dissertation further explored the relationships between patterns of eating, VAT, and mortality through three distinct studies. Exploration of the Healthy Eating Index-2015 (HEI-2015) scores among the Multiethnic Cohort (MEC) examined the association between HEI-2015 scores and risk of all-cause and cause-specific mortality. A pilot study was conducted to determine the effects of intermittent energy restriction combined with a Mediterranean diet (IER+MED) compared to an active comparator, a euenergetic Dietary Approaches to Stop Hypertension (DASH) diet, on VAT reduction among East Asian American adults. Assessing the association between Healthy Eating Index-2010 (HEI-2010) scores, VAT and overall adiposity among a multiethnic adult population constituted the third study. These studies were completed using observational and interventional designs. For the HEI-2015 study, the primary analysis was a survival analysis among MEC participants followed over a 17-22 y period. The IER+MED study was a randomized study where participants followed the prescribed diets over 12 weeks. The HEI-2010 study was cross-sectional and used DXA-based VAT. Among the MEC sample, comparing those with the highest quality diets to those with the lowest quality, the reduction in risk of mortality from all-cause, CVD, and cancer was 21%, 24%, and 20%, respectively, for men and 21%, 25%, and 16%, respectively, for women. Those following the IER+MED had significantly larger reductions in DXA-derived VAT and total fat mass (−22.6 ± 3.6 cm^2 and −3.3 ± 0.4 kg, respectively) vs. DASH (−10.7 ± 3.5 cm^2 and −1.6 ± 0.4 kg) ($p = 0.02$ and $p = 0.005$). For the HEI-2010 study, BMI, percent body fat, total body fat, trunk fat, insulin, and HOMA-IR were inversely related to HEI-2010 scores (all p values < 0.004). Findings from this dissertation support following a healthy dietary pattern is associated with lower VAT, and a reduced risk of mortality from all-causes, CVD, and cancer. In particular, IER+MED, may help to lower VAT and improve liver function.

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LIST OF ABBREVIATIONS

AARP	NIH-AARP Diet and Health Study
AHEI-2010	Alternative Healthy Eating Index-2010
ALT	Alanine transaminase
aMED	alternate Mediterranean Diet
AMPM	Automated Multiple-Pass Method
ASA24	Automated Self-Administered 24-hour dietary recall
AST	Aspartame transaminase
BMI	Body mass index
CER	Continuous energy restriction
CI	Confidence interval
CT	Computed tomography
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DGA	Dietary Guidelines for Americans
DHQ II	Diet History Questionnaire II
DPMP	Dietary Patterns Methods Project
DRI	Dietary Reference Intakes
DXA	Dual X-ray absorptiometry
EAR	Estimated average requirement
EASD	European Association for the Study of Diabetes
EASL	European Association for the Study of Liver
EASO	European Association for the Study of Obesity
EER	Estimated energy requirements
FFQ	Food frequency questionnaire
GLM	General linear model
GSLTPAQ	Godin-Shephard leisure-time physical activity questionnaire
HC	Hip circumference
HDL	High-density lipoprotein
HDLS	Healthy Diet and Lifestyle Study
HEI-2010	Healthy Eating Index-2010
HEI-2015	Healthy Eating Index-2015
HHS	Health and Human Services
HR	Hazard ratio
ICD10	International Classification of Diseases, Tenth Revision
ICD9	International Classification of Diseases, Ninth Revision
IER	Intermittent energy restriction
IER+MED	Intermittent energy restriction combined with a Mediterranean diet
IRB	Institutional Review Board
ISAK	International Society for the Advancement of Kinanthropometry
LA	Los Angeles
LDL	Low-density lipoprotein
MEC	Multiethnic Cohort
MEC-APS	Multiethnic Cohort Adiposity Phenotype Study
MED	Mediterranean
mFR™	Mobile food record
MPED	MyPyramid Equivalents Database
MRI	Magnetic resonance imaging
MUFA	Mono-unsaturated fatty acid
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NHOPI	Native Hawaiian or Other Pacific Islander
OR	Odds ratio
PAL	Physical activity level
PBRC	Pennington Biomedical Research Center

PREDIMED	Prevención con Dieta Mediterránea
PAQ	Physical activity questionnaire
PUFA	Poly-unsaturated fatty acid
QFFQ	Quantitative food-frequency questionnaire
REDCap	Research Electronic Data Capture
RR	Relative risk
SAT	Subcutaneous adipose tissue
SD	Standard deviation
SEM	Standard error of the mean
SFA	Saturated fatty acid
T1	Tertile 1
T2	Tertile 2
T3	Tertile 3
UCSF	University of California San Francisco
UHCC	University of Hawaii Cancer Center
USDA	United States Department of Agriculture
VAT	Visceral adipose tissue
VAT/SAT	Visceral adipose tissue/ subcutaneous adipose tissue ratio
WC	Waist circumference
WHI-OS	Women's Health Initiative Observational Study
WHR	Waist-hip ratio
WHtR	waist-to-height ratio
HRT	Hormone-replacement therapy

CHAPTER 1. DISSERTATION OVERVIEW

1.1 Introduction

Approximately 133 million people in the US suffer from a chronic disease [1-4], and this number continues to increase [1]. Along with the high cost of managing these conditions, heart disease, cancer, chronic obstructive pulmonary disease, diabetes, and stroke are responsible for more than two-thirds of deaths in the US [1,4]. Diet, physical activity, and tobacco use are modifiable risk factors with the most considerable influence on chronic disease [5]. This dissertation will focus on the effect of diet on risk for chronic disease and mortality.

Traditionally researchers studied the relationships between single foods or nutrients and health outcomes; however, diet is a complex mixture of foods and nutrients [6,7]. More recently there has been a shift to studying the relationship between dietary patterns, chronic disease, and mortality [6,7]. Dietary patterns take into account the synergistic effect of foods and nutrients on health [6,7]. Also, if the effect of foods consumed as part of a dietary pattern is cumulative, the impact on health outcomes may be more extensive and therefore, easier to detect [6,7]. There is substantial evidence demonstrating the beneficial effects of the Mediterranean-style (MED) diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and patterns of eating recommended by the Dietary Guidelines for Americans (DGA)[8-11]. Each of these dietary patterns have unique features and close adherence to each has been associated with a reduced risk of mortality from all-causes, cardiovascular disease (CVD), and cancer [12].

The relationships between diet quality and risk of chronic disease morbidity or mortality have been examined across interventional and observational studies [11]. In order to score compliance to the MED diet, DASH diet, and the DGA, a priori, or theoretically based scoring systems have been developed [8-10]. For this dissertation, the a priori index of focus is the Healthy Eating Index (HEI), in particular, the Healthy Eating Index-2010 (HEI-2010), and Healthy Eating Index-2015 (HEI-2015), which score adherence to the DGA 2010, and the DGA 2015-2020, respectively [9,13]. Given the relatively recent release of the HEI-2015, there are limited studies that have used this index. This dissertation examined the relationships between HEI-2015 scores, and risk of all-cause, CVD, and cancer mortality, which will contribute to the evidence base of this most recent translation of the DGA.

Studying visceral adiposity has become a research priority, as higher levels of visceral adipose tissue (VAT) are associated with greater risk of CVD [14], type 2 diabetes [15,16], certain cancers [17-19] and mortality [20-22]. Determinants of VAT include age [23-25], sex [23,25,26], physical activity [23,27], ethnicity [23,25], alcohol intake [28], and diet [23,29-31]. With advancing age, there are increases in VAT for both men and women across ethnic groups [24]. In regards to ethnicity, ethnic/racial heterogeneity, has been found to influence the propensity for VAT storage over subcutaneous adipose tissue (SAT) [32,33]. Higher diet quality has been shown to be inversely related to VAT and researchers have also reported higher intakes of medium-chain triglycerides, dietary fiber, calcium, and phytochemicals being associated with reduced VAT levels [29,30].

There is limited research on the effect of following the MED diet, DASH diet, and dietary patterns derived from the DGA on VAT levels. However, studies in this area demonstrate that following any of these patterns more closely is inversely related to VAT levels [30,34,35]. Intermittent energy restriction (IER) is an emerging pattern of eating that has shown promise

to reduce body fat and insulin resistance [36,37]. IER includes periods of marked energy restriction on at least one day (typically 60–75% below estimated energy requirements) but no more than six days per week, interspersed with periods of regular or ad libitum energy intake [38-42]. This dissertation will explore the association between HEI-2010 scores and VAT, and the effect of IER combined with a MED (IER+MED) diet vs. an active comparator (a euenergetic DASH diet) on reducing VAT. This dissertation does not cover validation of compliance to the MED or DASH diets.

1.2 Problem Statement

Closer adherence to the MED diet, DASH diet, and dietary patterns derived from the DGA is associated with a reduced risk of morbidity and mortality from chronic disease in the US [12]. A prori indices are among methods used in research to demonstrate this reduced risk [6]. As new a priori indices are introduced, to correspond with updates to dietary guidelines, these indices need to be tested to ensure prediction of health outcomes [9,13].

High VAT is a risk factor for chronic disease morbidity and mortality [14,34]; however, there are no known clinical guidelines for preventing or managing VAT. There is also limited research assessing the relationship between diet quality and VAT. Therefore, further research is needed to explore the effects of following a high quality diet on VAT amongst adults in the US.

1.3 Objectives

Objective 1: Examine the association between the HEI-2015 and mortality from all-causes, CVD, and cancer in the Multiethnic Cohort (MEC), which represents a large cohort of adult men and women representing five distinct ethnic groups residing in Hawaii and Los Angeles (LA).

Objective 2: Demonstrate the feasibility to conduct an intermittent energy restriction combined with a MED (IER+MED) diet vs. an active comparator (a euenergetic DASH diet) randomized interventional pilot study to reduce VAT among East Asian Americans in Hawaii; evaluate study retention and protocol adherence, and explore the differences between IER+MED and DASH diet groups with regard to total adiposity and metabolic risk biomarkers.

Objective 3: Examine the cross-sectional association between diet quality (HEI-2010 scores) and DXA-based VAT, overall adiposity, and blood-based biomarkers of metabolic risk, among a multiethnic adult population.

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CHAPTER 2. LITERATURE REVIEW

This literature review will explore methods for assessing dietary intake data to establish quantitative estimates of nutrients and foods, examine the influence of dietary patterns in interventional and observational studies, and summarize key study designs and outcome measures used to quantify the effect of dietary patterns on health outcomes. The aim of this review is to provide essential background information and rationale for conducting the three research studies making up this dissertation.

2.1 Methods of Assessment to Quantify Dietary Intake

This section will concentrate on methods of collecting self-reported dietary intake at the individual level for use in group-level analyses in a research study. Collecting information on foods and beverages consumed allows researchers to assess the relationship between dietary intake and health. Assessment methods covered include; dietary records (with focus on the mobile food record (mFR™)), 24-hour dietary recall, and food frequency questionnaire (FFQ). Greater detail will be provided on the mFR™ and FFQ as these methods were used to collect dietary data in research studies comprising this dissertation.

Traditional dietary records provide detailed descriptions of food and beverages consumed and allow for assessment of usual diet in research studies [1]. Participants are trained to record (and sometimes weigh) intakes of food and beverages in real-time [2], and add detailed information on brands, ingredients, portion size, and cooking preparation methods [3]. Consequently, participants must be highly motivated and literate [3]. This potential for selection bias may limit the generalizability of research results to the general population [3]. Theoretically, completing dietary records in real-time reduces the reliance on memory to recall foods eaten [3]. However, if participants forget to record a food or beverage consumed, intake is recorded retrospectively [3]. On completion, a trained interviewer should review dietary records to check for completeness and probe for missing food items [4].

The level of detail and diversity of dietary data collected is a strength of the dietary record. A limitation of this assessment method is reactivity bias [5]. For example, recording foods consumed in real-time may increase participants' self-awareness of their intakes and influence their eating behaviors [5]. Therefore, dietary records may not be representative of a participant's regular diet [5]. However, this reactivity bias may be beneficial in studies where the goal is behavior change (e.g., weight loss studies) [6]. Underestimation of energy from dietary records has been reported to be approximately 18% to 37% among adult men and women [7-10]. Under-estimation of energy intake from dietary records is known to be higher for women [11] and people with a higher BMI [11,12], which may be due to dieting behaviors among these groups [13]. Another limitation of dietary records is the time and cost required to train study staff to code and enter dietary data into a nutrient database [3].

Advances in technology have led to the development of image-based methods for collecting dietary records, including the mFR™ [9,14-16]. These advanced technologies may help reduce the user and technician burden, cost, and improve the accuracy of dietary records [1,2]. The mFR™ is designed to capture images of foods/beverages before and after (to record waste) each eating occasion and allows for automatic uploading of images to a secure cloud-based server when in 3G/4G/Wi-Fi range [9,14-16]. The mFR™ app can be loaded onto a participant's mobile device or a study mobile device [17,18]. Participants are trained on how to use the mFR™ and are provided with a fiducial marker (a small reference device of known

dimensions and colors) to include in images [9,16]. Images from the mFR™ can be reviewed in person or remotely via the cloud-based server [17,18].

Unlike traditional methods, when participants use the mFR™, there is no need to weigh and write down details of food and beverages consumed. Removing these tasks may help improve the usability of dietary records [9,16], and allows groups with lower literacy to participate in the research (e.g., children [19], people with Down syndrome [20]). Under-reporting of energy intake using the mFR™ has been reported as 12% and 10% for adult men and women, respectively, which is comparable to traditional dietary records [9]. Portion size and identification of food and beverages in images is conducted manually by a trained staff or automated methods [21]. Limitations of the mFR™ include; participants need to remember to take before and after eating images, include the fiducial marker in each image, and take high-quality images (e.g., not blurry) [16,22].

Other dietary records include; wearable cameras, handheld digital cameras, and mobile apps with additional details on food and beverages consumed added by text or audio by participants [22]. These dietary record methods were not used in this dissertation.

The FFQ estimates daily intakes over a more extended time, e.g., past week, month, or year [23,24]. FFQs vary in length (e.g., ~100 to 200 questions). Participants select foods consumed from the listed food items, and in the case of a quantitative FFQ, the participants also select the frequency the food was consumed [3]. The foods listed can be single food items (e.g., beans), or mixed dishes (e.g., chili) [3]. In general, FFQs collect less detailed information than other assessment methods (e.g., 24-hour recalls and dietary records). Given this, FFQs are generally more appropriate for ranking participants according to food or nutrient intakes rather than estimating actual intakes [3]. However, if a FFQ is designed to assess total diet, it will generally list a higher number of food and beverages, with additional questions on portion size [3]. Due to the finality of items listed in a FFQ, the food and beverages listed need to be appropriate for the target population being assessed [25,26]. For example, the FFQ used for the Multiethnic Cohort study (MEC) was developed and validated for five ethnic groups; i.e., white, African American, Japanese American, Latino and Native Hawaiian [27]. The FFQ must also align with food and beverages listed in a nutrient database to allow for accurate analysis of the questionnaire [3,27]. For the MEC, an ethnic-specific food composition database was developed to allow for analysis of FFQ data [27].

Compared to other dietary assessment methods, FFQs are relatively simple, cost-efficient, and time-efficient to administer and analyze [3,24]. For example, most FFQ are self-administered either electronically or by paper-and-pencil, and completed FFQs can be scanned electronically for analysis [3,28,29]. Consequently, a FFQ is ideal for large epidemiology studies [24,29]. Limitations of the FFQ include this method relies heavily on cognitive ability to recall foods consumed, and is associated with significant measurement error [3]. FFQs have been found to under-report energy intake by up to 36% in adults [3,30-33]. This measurement error can be reduced by handling missing data appropriately, adjusting for energy intake, and regression-calibration [2,27,34-36].

The 24-hour dietary recall is used to assess total diet, and asks participants to recall everything eaten in the previous 24 hours [3]. This assessment method can be interviewer-administered, and interviewers need to be highly trained to probe for additional details (e.g., brands, ingredients, preparation methods, time consumed), and missing food items [37,38]. The most advanced interview-administered 24-hour dietary recall method in the US is the US Department of Agriculture's (USDA) Automated Multiple-Pass Method (AMPM)[39,40].

Alternatively, 24-hour recalls can be administered electronically, e.g., using the Automated Self-Administered 24-hour dietary recall (ASA24) [41]. Research has found that results from the AMPM and the ASA24 are comparable, but which assessment tool is used is dependent on the research study design [42]. If participants have higher literacy, including computer literacy, the ASA24 would be an appropriate tool. For those with lower literacy, the AMPM may be more suitable as an interviewer can record details provided by the participant [3]. For larger studies, the ASA24 may be more appropriate as responses are automatically coded on entry; whereas, responses from the AMPM require manual coding and entry [3].

Similar to dietary records, for the 24-hour recall, women, and people of higher BMI tend to have higher under-reporting [13,43,44]. Under-reporting of energy intake with 24-hour recalls ranges from 3-34% among adults [3,30,40,44]; however, adjusting for energy intake helps to correct for this error [43].

In this dissertation, collection of dietary data using the mFR™ and FFQs allowed for diet as an exposure to be analyzed.

2.2 Examining Diet Using Dietary Patterns

Traditionally researchers studied the relationship between single foods or nutrients and estimated health outcomes; however, diet is a complex mixture of foods and nutrients [45,46]. More recently there has been a shift to studying dietary patterns as an exposure [45,46]. Dietary patterns take into account the synergistic effect of foods and nutrients on health [45,46]. Also, if the effect of foods consumed as part of a dietary pattern is cumulative, the impact on health outcomes may be larger and therefore, easier to detect [45,46]. An example of a dietary pattern is the Mediterranean (MED) diet. The MED diet represents the traditional food habits of individuals living around the Mediterranean Sea [47,48]. It is primarily a plant-based diet rich in olive oil, olives, fruits, vegetables, whole grains, legumes and nuts with moderate amounts of dairy products (principally cheese and yogurt), fish, poultry, red wine, and limited amounts of red meat [47-49]. Other dietary patterns explored as exposures in this dissertation are the Dietary Approaches to Stop Hypertension (DASH) diet [50,51], patterns derived from the Dietary Guidelines for Americans (DGA) 2010 [52] and the DGA 2015-2020 [47], and intermittent energy restriction (IER) [53].

Diet indices are one method used to measure compliance to following dietary patterns [46,54-56]. This dissertation incorporated a priori diet indices, which are theoretically driven dietary patterns [45,46]. These include the Healthy Eating Index-2010 (HEI-2010)[56], and the Healthy Eating Index-2015 (HEI-2015)[57], which score compliance to the DGA 2010 and the DGA 2015-2020, respectively. Also, a priori indices for the DASH diet and the MED diet will be discussed as the MED and DASH diets were used as dietary guidance in research that makes up this dissertation. Alternative methods for assessing dietary pattern exposures, not adopted in this dissertation, include data-driven indices (predominantly through cluster analysis, principal component, factor analysis, or reduced rank regression) [46,58-61].

As the MED diet represents the food habits of individuals in the Mediterranean region, it is not a single eating pattern, but a style of eating [48,52,62]. The Lyon Diet Heart Study and the Prevención con Dieta Mediterránea (PREDIMED) cohort are the only two long-term intervention studies providing evidence on the health benefits of the MED diet [49,63-65]. In the Lyon Diet Heart Study, participants were randomized to a Western-style diet or a Mediterranean-style diet for 104 weeks [49,65,66]. The study was stopped early because participants following the MED diet had a 50-70% lower risk of cardiac events compared to

the control group (the Western-style diet) [49,64]. In the PREDIMED study, participants were randomized to a MED diet supplemented with extra virgin olive oil, a MED diet supplemented with nuts, or to the control group following a low-fat diet [63,64]. The 2018 reanalysis of the PREDIMED study demonstrated that the MED groups had a significantly lower risk of stroke, myocardial infarction, and cardiovascular disease (CVD) mortality, compared to the control group [63].

Many a priori dietary patterns have been used in observational studies to assess compliance to the MED diet, the most common being the MDS developed by Trichopoulou et al. [67,68], and the Alternative Mediterranean diet (aMED) score [69,70]. The MDS has nine components including; vegetables, fruits and nuts, legumes, fish and seafood, meat and meat products, cereals, dairy products, moderate alcohol intake, and the ratio of MUFA to SFA [67]. Scores range from 0-9 points, with higher scores representing diets more in line with the traditional MED diet [67]. The aMED score is similar to the MDS; however, was adapted for use among the US population [69,71]. Consistently, observational studies employing these diet indices have reported greater adherence to a MED diet being associated with a significant reduction in risk of CVD, morbidity, or mortality [72,73]. This evidence has led to the MED diet being one of the recommended healthy dietary patterns for the US population to follow in the 2015-2020 DGA [47]. The MED diet is promoted for the management of non-alcoholic fatty liver disease (NAFLD) in joint clinical practice guidelines issued by the European Associations for the Study of Liver (EASL), Diabetes (EASD) and Obesity (EASO) [74]. Also, the MED diet may help to reduce other ectopic fat stores, including visceral adipose tissue (VAT) [75,76]. This research area will be explored in Chapter 4.

The DASH diet is rich in fruit, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts, and limits total fat, saturated fat and sodium, and is recommended by the American College of Cardiology and the American Heart Association for the reduction of low-density lipoprotein (LDL) and blood pressure [50,51,64,77]. Intervention studies have shown following the DASH diet is associated with decreased systolic and diastolic blood pressure, total cholesterol, LDL, HbA1c, fasting blood insulin, and body weight [78]. The effect of DASH on blood pressure may be greater when sodium is restricted [50], or when the macronutrient composition is altered (e.g., higher protein, or higher ratio of unsaturated fat) [79]. DASH has proven to be helpful for normotensive people; however, it may have a more significant effect on lowering blood pressure in people with hypertension [50]. Like the MED diet, the DASH diet is recommended as a healthy dietary pattern in the 2015-2020 DGA [47]. Across prospective cohort studies DASH is associated with decreased risk of CVD, coronary heart disease, stroke, and diabetes [78]. An a priori DASH index is one method used to obtain these findings [80]. There are multiple versions of the DASH index; however, the DASH index by Fung and colleagues is the version used in the Dietary Patterns Methods Project (DPMP); therefore, relevant to this dissertation [80,81]. The DASH index by Fung and colleagues is based on eight food and nutrients components that make up the DASH diet [80]. A higher DASH score is achieved by greater intakes of fruits, vegetables, nuts and legumes, whole grains, low-fat dairy, and by consuming less sodium, red and processed meats, and sweetened beverages [80]. To add to the evidence for using dietary patterns to guide dietary advice, the National Cancer Institute (NCI) initiated the DPMP [83,84]. The DPMP is a collaborative project between three large cohort studies, including the NIH-AARP Diet and Health Study (AARP) [85,86], the Multiethnic Cohort Study (MEC) [29,87], and the Women's Health Initiative Observational Study (WHI-OS) [88,89]. These groups adopted overlapping and

complementary research questions and have conducted a standardized diet analysis using four dietary indices, including DASH [84]. Results from the DPMP highlighted greater adherence to DASH was consistently associated with a reduced risk of death due to all-causes, CVD, and cancer compared to those with the lowest adherence to the diet [84].

The DGA are evidence-based guidelines that guide all federally funded nutrition programs in the US [47,90], including; food policies, food assistance programs, and education programs [90]. The DGA were first released in 1980, and a federal mandate specifies updates every five years [90]. In 1995, an a priori index, the HEI, was introduced to assess compliance to the DGA recommendations [91]. To match updates to the successive dietary guidelines, the NCI developed the HEI-2005 [92], HEI-2010 [56], and HEI-2015 [57]. These indices have provided a tool to evaluate the strength of the DGA recommendations [57]. The HEI-2015 consists of 13 components, and the maximum HEI score is 100 points [57]. There are nine adequacy components (foods to eat enough of) including Total Fruits, Whole Fruits, Total Vegetables, Greens and Beans, Whole Grains, Dairy, Total Protein Foods, Seafood and Plant Proteins, and Fatty Acids [57]. There are four moderation components (foods to limit), including Refined Grains, Sodium, Added Sugars, and Saturated Fats [57]. The Alternate Healthy Eating Index (aHEI) is an adaption of the original HEI developed by McCullough and colleagues in 2002 [93], and later updated by Chiuve and colleagues in 2012 [94].

A systematic review and meta-analysis, with all HEI versions up until the HEI-2010, found that people with the highest diet quality (highest HEI scores) were at significantly lower risk of all-cause mortality, CVD, cancer, type 2 diabetes, and neurodegenerative disease [81]. This systematic review included subgroup analyses with the different versions of the HEI, and found that the inverse association between HEI scores and cancer incidence was only seen for the HEI-2005 and HEI-2010 versions [81]. This may be due to the scoring differences between these HEI indices (e.g., the original version of the HEI did not score refined and unrefined grains separately) [81]. Given the relatively recent release of the HEI-2015, there are limited studies that have used this index to assess the relationship between diet quality and health outcomes. Research evaluating the predictive validity of the HEI-2015 will be covered in Chapter 3 of this dissertation.

IER is an emerging pattern of eating that is becoming more widely studied [53,95,96]. IER includes periods of marked energy restriction on at least one day (typically 60–75% below estimated energy requirements) but no more than six days per week, interspersed with periods of regular or ad libitum energy intake [53,97-100]. Harvie et al. suggested combining two consecutive days of IER with five days of a MED type diet (IER+MED) to promote satiety and high-quality nutrition [95]. Long term adherence to daily energy restriction, also known as continuous energy restriction (CER), is known to be challenging [101]. Therefore, IER was developed as an alternative method of energy restriction for weight loss and to help optimize health outcomes [53,101]. Currently, there is no a priori index to measure compliance to IER. However, total energy restriction and percentage energy from macronutrients can be used to measure compliance with dietary prescriptions during IER interventions [95]. IER, as a method for reducing visceral adiposity, will be discussed in this dissertation in Chapter 4.

2.3 Quantifying the Effect of Dietary Patterns on Health Outcomes

In order to explore the merits of dietary patterns, multiple study designs, and multiple outcome measures can be used. The study designs and outcome measures used in this

dissertation to assess the relationship between diet quality, VAT, and risk of mortality will be the focus of this section.

The MEC is a prospective cohort study. MEC was used in this dissertation to assess whether diet quality (HEI-2015 scores) influenced the risk of mortality over a 17-22 y follow-up. Cohort studies are one of the strongest study designs to help minimize bias and infer causality between dietary patterns and mortality [102]. Cohort studies generally enroll people who are disease-free at baseline, assess baseline measures, and follow the participants over time until an event of interest; e.g., death [3]. A limitation of using cohort studies is that they are time and resource-intensive to administer due to the large sample size required and study duration [3].

The Healthy Diet and Lifestyle Study (HDLS) intervention, detailed in Chapter 4 of this dissertation, adopted a randomized active comparator design. Intervention studies generally take measures across at least two periods (e.g., baseline and the end of the intervention) and are useful for demonstrating the effect of diet on change in health outcomes [3]. Randomized control trials are the gold standard intervention study design [103]. In order to reduce attrition and to ensure all participants receive some treatment of care, a randomized active comparator study can be used [104,105]. For active comparator designs, the comparison group is assigned a diet that is known to be beneficial but is different from the primary intervention diet [63,104,105]. In HDLS, the healthful diet assigned to the active comparator group was a euenergetic DASH diet.

The analysis of Shape Up! Adults, detailed in Chapter 5 of this dissertation, was a cross-sectional study. Cross-sectional studies can be used to describe population characteristics, for surveillance, evaluate adherence to dietary guidelines, and to examine the association between diet and disease [3]. In a cross-sectional study, measurements are collected on a group of participants at a single point in time [3]. This study design is relatively fast and inexpensive because of the one-time measurement of exposure and disease [106]. Measuring diet and disease at the same time is also a limitation as there is no temporality [106]. Consequently, causality between an exposure and health outcomes can not be determined by cross-sectional studies [106]. However, information provided from cross-sectional studies is useful for planning cohort and intervention studies [106], and these studies can used to support causality between diet and disease [3,107].

Anthropometric methods are commonly used in nutrition research, as they are relatively inexpensive and simple to administer [108]. In the MEC HEI-2015 study, anthropometric data were used to calculate and control for BMI in mortality analyses. In HDLS and the Shape Up! Adults study, anthropometric measures were used to assess the effect of dietary patterns on health outcomes.

In order to collect accurate anthropometric measures, the International Society for the Advancement of Kinanthropometry (ISAK) protocols should be followed [109,110]. In the literature, anthropometric measures used as predictors of VAT include waist hip ratio, BMI, waist circumference [111,112], and more recently, the waist-to-height ratio (WHtR) [112]. Using a combination of both BMI and waist circumference is the most accepted method to approximate VAT [113]. In research assessing the association between dietary patterns and VAT, waist circumference has most commonly been used as the surrogate measure of VAT [75]. It has been noted that VAT correlates more strongly with waist circumference in men vs. women adults, and white vs. Asians [114]. These differences need to be taken into consideration in dietary pattern analyses among multiethnic groups of men and women.

DXA is a laboratory-based method used to measure VAT, and was the method adopted in both the HDLS and Shape Up! Adults study. Magnetic resonance imaging (MRI) and computed tomography (CT) are considered the "gold standard" for measuring VAT, [111,115,116]; however, with advances in DXA, DXA-based VAT has become an acceptable measure [75]. Both MRI and CT provide high-resolution cross-sectional scans and measures of SAT, VAT, bone, muscle, and viscera [109,117]. MRI does not expose participants to radiation; however, they are expensive and take a relatively long time to perform [109,117]. CT scans do expose participants to radiation; therefore, they are not suitable for children and pregnant women [109,117]. New DXA-based methods of measuring VAT strongly correlates with CT and MRI and can be performed more efficiently and with a low exposure of radiation to both the participant and examiner [116,118]. After the DXA scan, software allows for the calculation of VAT [118]. For example, VAT in the L4-L5 region can be estimated by calculating the difference between total body fat and subcutaneous adipose tissue (SAT) [118]. The limitation of this method is DXA can underestimate VAT in lean individuals and overestimate VAT in individuals with high VAT levels [118,119]. Experts encourage the continued use of DXA-based measures in VAT research [75].

VAT is a biomarker for risk of CVD, type 2 diabetes, certain cancers, and mortality [120-125]. A biomarker is a measure of normal biological processes, and can be used to measure biochemical or physiological response, the clinical endpoint, or risk of the clinical endpoint [126]. In HDLS and the Shape Up! Adults study, VAT was used to estimate the effect of dietary patterns on health outcomes. Biomarkers should be relatively easy and non-invasive to obtain, and they are useful to show the short term effect of an intervention [126]. In the case of VAT, researchers can monitor change in VAT over a shorter time frame, versus following participants until the onset of disease/death [76,127]. Often it is better to use more than one biomarker to provide a more thorough assessment [126]. For example, in addition to VAT, other biomarkers of metabolic dysfunction monitored in HDLS and Shape Up! Adults included blood pressure, HDL, triglycerides, and HbA1c.

2.4 References

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CHAPTER 3. TESTING THE PREDICTIVE VALIDITY OF THE HEALTHY EATING INDEX-2015 IN THE MULTIETHNIC COHORT: IS THE SCORE ASSOCIATED WITH A REDUCED RISK OF ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY?

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3.1 Abstract

The Healthy Eating Index-2015 (HEI-2015) was created to assess conformance of dietary intake with the Dietary Guidelines for Americans (DGA) 2015–2020. We assessed the association between the HEI-2015 and mortality from all-cause, cardiovascular disease (CVD), and cancer in the Multiethnic Cohort (MEC). White, African American, Native Hawaiian, Japanese American, and Latino adults (n > 215,000) from Hawaii and California completed a quantitative food-frequency questionnaire at study enrollment. HEI-2015 scores were divided into quintiles for men and women. Radar graphs were used to demonstrate how dietary components contributed to HEI-2015 scores. Mortality was documented over 17–22 years of follow-up. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed using Cox proportional hazards models. High HEI-2015 scores were inversely associated with risk of mortality from all-cause, CVD, and cancer for men and women (p-trend <0.0001 for all models). For men, the HRs (CIs) for all-cause, CVD, and cancer comparing the highest to the lowest quintile were 0.79 (0.76, 0.82), 0.76 (0.71, 0.82), and 0.80 (0.75, 0.87), respectively. For women, the HRs were 0.79 (0.76, 0.82), 0.75 (0.70, 0.81), and 0.84 (0.78, 0.91), respectively. These results, in a multiethnic population, demonstrate that following a diet aligned with the DGAs 2015–2020 recommendations is associated with lower risk of mortality from all-cause, CVD, and cancer.

3.2 Introduction

Dietary pattern analysis is a relatively new method to quantify diet quality, monitor changes in population-based diet quality, and assess the relationships between diet quality and health-related outcomes [1–4]. Analyses of individual nutrients and foods are still important; however, as we consume foods in combination, the synergistic effect of food on health must be considered [2]. Studying diet patterns also allows researchers to promote

dietary recommendations in the form of patterns, which may be easier for the general public to interpret and follow [5].

Dietary indices are important tools used to assess dietary patterns. They may be derived from theoretically based scoring systems or a priori approaches, which are guided by evidence-based research [2]. For example, the Healthy Eating Index (HEI) is constructed to reflect the evidence-based recommendations of the Dietary Guidelines for Americans (DGA) and to evaluate conformance to these recommendations [6–9]. Every five years the Dietary Guidelines Advisory Committee reviews current nutrition research and provides an Advisory Report to the United States Department of Agriculture (USDA) and Health and Human Services (HHS) [4,10]. Guided by this report, the USDA and HHS publish the Dietary Guidelines for Americans (DGA), which provide evidence-based food and beverage recommendations to the public [4,10]. Since the implementation of the original HEI in 1995, development and application of successive HEIs to assess and monitor dietary status have been ongoing [3,6,11]. The HEI-2005 introduced density-based scoring standards, which were continued in the HEI-2010 and HEI-2015. Additional changes to scoring standards were implemented between each new HEI to reflect updates in the DGA [3,12,13].

To add to the evidence for using dietary patterns to guide dietary advice, the National Cancer Institute (NCI) initiated the Dietary Patterns Methods Project (DPMP) [13–15]. This is a collaborative project between three large cohort studies, including the NIH-AARP Diet and Health Study (AARP) [16,17], the Multiethnic Cohort Study (MEC) [18,19] and the Women's Health Initiative Observational Study (WHI-OS) [20,21]. These groups adopted overlapping and complementary research questions and conducted standardized diet analysis using four dietary indices, including the HEI-2010, the Alternative Healthy Eating Index-2010 (AHEI-2010), the alternate Mediterranean Diet (aMED), and the Dietary Approaches to Stop Hypertension (DASH) [15]. A summary of the results revealed that men and women with higher quality diets (higher index scores) were at significantly lower risk (11–28%) of death from all-causes, cardiovascular disease (CVD), and cancer compared to people with lower quality diets (lower index scores) [15]. This was true for mortality assessments made with each dietary index, with the exception of women from the WHI-OS cohort, where the AHEI-2010 score was not associated with cancer death [15].

The HEI-2015 was introduced to reflect the DGA 2015–2020 [12]. The HEI-2015 is comprised of 13 components and the maximum HEI score is 100 points [12]. There are nine adequacy components (foods to eat enough of) including Total Fruits, Whole Fruits, Total Vegetables, Greens and Beans, Whole Grains, Dairy, Total Protein Foods, Seafood and Plant Proteins, and Fatty Acids. There are four moderation components (foods to limit) including Refined Grains, Sodium, Added Sugars, and Saturated Fats. Most components are scored on a density basis, that is, amounts per 1000 kcal of intake [12]. The Fatty Acids component is scored using the ratio of poly- and mono-unsaturated fatty acids (PUFAs and MUFAs) to saturated fatty acids (SFAs), and Added Sugars and Saturated Fats are scored as a percentage of total energy intake. The key differences between the HEI-2010 and the HEI-2015 include the scoring for legumes and the Empty Calories component. In the HEI-2010, legumes were allocated into two components and have expanded into four components with the HEI-2015, including Total Vegetables, Greens and Beans, Total Protein Foods, and Seafood and Plant Proteins [12]. In the HEI-2015, the Empty Calories single component was replaced with the two components of Saturated Fat and Added Sugars [12]. Alcohol is no longer included in the

Empty Calories component score; instead, the energy (kcal) from alcohol is now added to the total energy intake per day [12].

To assess the efficacy of the new HEI score, the AARP, MEC, and the WHI-OS each completed a standardized mortality assessment using the HEI-2015. The aim of this study is to examine the association between the HEI-2015 and mortality from all-cause, CVD, and cancer in the MEC, which represents a large cohort of adult men and women from five distinct ethnic groups residing in Hawaii and Los Angeles (LA).

3.3 Methods

3.3.1 Study Population

The MEC is a large prospective cohort study developed to investigate the relationship between diet and health-related outcomes among African American, Latino, Japanese American, Native Hawaiian, and white men and women [18]. Hawaii and the LA basin have large multiethnic populations; therefore, participants were recruited from these areas between 1993 and 1996. A detailed report of the MEC study design and implementation has previously been published [18]. Briefly, inclusion criteria were men or women, 45–75 years and living in Hawaii or LA at cohort entry. Driver's license files were the primary resource used to identify potential participants. Secondary resources included voter registration and Medicare files. The final sample included over 215,000 individuals, who identified as African American (16.2%), Latino (21.2%), Japanese American (26.4%), Native Hawaiian (6.7%), white (23%) or other ancestry (6.5%). Socio-demographic, anthropometric, health history, physical activity and dietary intake information were collected at cohort entry using a 26-page self-administered questionnaire (Qx1). The institutional review boards at the University of Hawaii and the University of Southern California approved the study.

3.3.2 Dietary Assessment and Calculation of the Healthy Eating Index-2015 (HEI-2015)

All participants were provided with the Qx1 written in English, and Latinos were provided English and Spanish language versions [18]. A detailed description of the development and validation of the Qx1 is published elsewhere [18,22]. The Qx1 included a quantitative food-frequency questionnaire (QFFQ), developed to be suitable for the five main ethnic groups in the study [18]. The QFFQ was validated and calibrated in each ethnic-sex group [22]. Dietary intake over the last year was assessed using 182 questions. Questions were grouped into key categories, e.g., meats, bread items, and alcoholic and other beverages. The frequency of consumption was assessed using ordinal categories ranging from "never or hardly ever" to "4 or more times a day". Serving sizes were also assessed using categories with the format varying by food. Images of different portion sizes were provided to help participants estimate the serving size of some food items, e.g., stir-fried beef. For other food items, three different written serving size options were provided without images, e.g., ½ hot dog, 1 hot dog, 2 hot dogs or more. A customized multiethnic food composition database was developed for the MEC [18,19,23]. This database was used to calculate food groups according to the MyPyramid Equivalents Database (MPED) [24,25]. The MPED is a system developed by the USDA to help researchers examine dietary data in terms of MyPyramid food groups (e.g., total vegetables, added sugars). Dietary intakes using the MyPyramid food groups were calculated from the QFFQ by summing each participant's daily servings across the food items. The HEI-2015 scores were calculated using the MPED group and subgroup data [24]. SAS

program code to calculate HEI-2015 scores was created specifically for the DPMP by the NCI to insure harmonization in coding across the cohorts participating in the DPMP project [14].

3.3.3 Healthy Eating Index-2015 (HEI-2015) Scoring

The HEI provides a score for diet quality and not diet quantity. For example, the index can provide information on the quality of the food consumed, but not whether an individual is meeting his or her nutrient requirements [13]. A quality versus quantity approach was chosen because it allows for the comparison of scores between age and sex groups [13]. An overview of HEI-2015 components and scoring standards can be found in Table 3.1. The HEI-2015 aligns with and reflects the changes between the 2010 DGA and 2015–2020 DGA [12]. The HEI-2010 and HEI-2015 have the following features in common: adequacy and moderation components, the same adequacy components, most components scored on a density basis, and standards for recommendations based on the least restrictive standards, e.g., least restrictive sodium recommendations [12]. As previously mentioned, scoring standards for legumes and the Empty Calories component have changed. Also, energy from alcohol consumed is now added to total energy intake per day for HEI-2015, which is used as the denominator for density values. This change results in a lower HEI-2015 score for an individual who consumes alcohol compared to an individual with the same diet who does not. For example, for the Total Fruits component, computed as (Total Fruits in cup equivalents per day/energy intake per day) × 1000 kcal) [13], will have a larger denominator for the individual who consumes alcohol, thereby decreasing the Total Fruits component score and HEI-2015 score.

To achieve the maximum HEI-2015 score of 100 points, an individual would need to score maximum points on all components. For each component, intakes closer to the DGA recommendations increase the score. Therefore, to achieve a perfect HEI-2015 score, individuals need to have a high intake of foods that count toward the adequacy components and a low intake of foods that count toward moderation components (moderation components are scored inversely). Scores between the minimum and maximum standards for each component are computed proportionately [3].

Table 3.1 Healthy Eating Index-2015 (HEI-2015) component scoring standards using standardized cup and ounce equivalents from the MPED [1,2,3].

Components	Maximum Scores	Standard for Maximum Scores [3]	Standard for Minimum of Zero
Adequacy			
Total Fruits [4]	5	≥0.8 cup	No Fruits
Whole Fruits [5]	5	≥0.4 cup	No Whole Fruits
Total Vegetables [6]	5	≥1.1 cup	No Vegetables
Greens & Beans [6]	5	≥0.2 cup	No Greens and Beans
Whole Grains	10	≥1.5 oz	No Whole Grains
Dairy [7]	10	≥1.3 cup	No Dairy
Total Protein Foods [6,8]	5	≥2.5 oz	No Protein Foods
Seafood & Plant Proteins [6,8]	5	≥0.8 cup	No Seafood & Plant Proteins
Fatty Acids [9]	10	(PUFAs + MUFAs)/SFAs ≥ 2.5	(PUFAs + MUFAs)/SFAs ≤ 1.2
Moderation			
Refined Grains	10	≤1.8 oz	≥4.3 oz
Sodium	10	≤1.1 g	≥2.0 g
Added Sugars	10	≤6.5% of energy	≥26% of energy
Saturated Fats	10	≤8% of energy	≥16% of energy

[1] Scoring standards are expressed as cup and ounce equivalents from the MyPyramid Equivalents Database (MPED), whereby 1 oz = 28.3 g and 1 cup = 225 mL. [2] Intakes between the minimum and maximum standards are scored proportionately. [3] All standards represent amounts per 1000 kcal, except for Fatty Acids, Added Sugars and Saturated Fats. [4] Includes 100% fruit juice. [5] Includes all forms expect juice. [6] Includes legumes (beans and peas). [7] Includes all milk products, such as fluid milk, yogurt, cheese and fortified soy beverages. [8] Includes seafood, nuts, seeds, and soy products (other than beverages). [9] Ratio of poly- and mono-unsaturated fatty acids (PUFAs and MUFAs) to saturated fatty acids (SFAs).

3.3.4 Case Ascertainment

Deaths were identified by using state death files and the National Death Index. Deaths from CVD were identified and classified as International Classification of Diseases, Ninth Revision (ICD9) codes 390–448 or International Classification of Diseases, Tenth Revision (ICD10) codes I00–I78 and G45 [26,27]. Cancer deaths were identified by using ICD9 codes 140–209 or ICD10 codes C00–C96 [26,27]. All-cause mortality included CVD and cancer deaths as well as deaths from other causes, including accidents and suicides. All death files were current as the closure dates of 31 July 2015 for participants in Hawaii and 31 March 2015 for participants in LA. Participants with no recorded deaths as of these closure dates were censored.

3.3.5 Statistical Analysis

Analyses were limited to 70,170 men and 86,634 women who identified with one of the five main MEC ethnic groups (white, African American, Japanese American, Native Hawaiian, and Latino) (excluding n = 13,992), had valid dietary assessment information (excluding n = 8263); and had no previous history of cancer, heart attack, or stroke at baseline (excluding n = 36,723). The association of all-cause, CVD, and cancer mortality with HEI-2015 was modeled separately for men and women through Cox regression using years since study entry as the time metric. Cox regression was run for all ethnic groups combined and for each ethnic group separately. To assess if any one particular component was driving the association of HEI-2015 with mortality outcomes, we examined separate Cox models for HEI-2015, removing one dietary component at a time [16]. The association of mortality outcomes with

the HEI-2015 was also modelled on the MEC sample with 17,012 fewer mortality cases from the follow-up period of the HEI-2010 mortality analysis [19]. Sensitivity analysis with the same number of cases as the previous study [19] was performed to compare the difference between HEI-2010 and HEI-2015, and so that any observed differences would not be influenced based on the additional mortality cases. For CVD and cancer models, study participants who died of other causes were censored at the time of death. The following self-reported covariates were included in all models: age at study entry and energy intake as continuous variables, history of diabetes (yes or no), ethnicity (as indicator variables), weekly hours of moderate-to-vigorous physical activity (<2.5 or ≥2.5 hours/week), smoking (current smoker, past smoker, or never smoked), education (<12, 12, 13–15, or ≥16 years) as a proxy of socioeconomic status, marital status (married or not married), and hormone-replacement therapy (HRT) (yes or no (women only)). BMI (in kg/m^2) was categorized as ≤24.9, 25–29.9, or ≥30 using self-reported height and weight. The HEI-2015 does not have a unique component for alcohol; therefore, models were further adjusted for alcohol intake in the past year as a continuous variable. All variables included as continuous measures had no missing values. Education, marital status, smoking, BMI, and weekly hours of moderate to vigorous physical activity had missing values; thus, each of these variables were modeled with a separate missing value category. Missing values ranged from <1% to 2.3% of the total sample. Separate models were fit for men and women with all ethnic groups combined. Total HEI-2015 scores and HEI-2015 with one component removed were divided into quintiles. HRs and 95% confidence intervals (CIs) were calculated for each quintile using the lowest quintile as a reference category. Wald's chi square statistic was used to evaluate the linear trend on the basis of the median dietary score within each quintile. The proportional hazards assumption for Cox models was verified by plotting scaled Schoenfeld's residuals against the time to the event [28]. Mean HEI-2015 scores by ethnic group and sex were compared using ANOVA. Given the ANOVA results were statistically significant for both men and women, post hoc analysis was undertaken using Scheffe's multiple comparisons procedure.

Radar graphs were constructed to provide a visual representation of how men and women in quintile 1 and quintile 5 obtained their overall HEI-2015 scores [29]. Each axis on a radar graph represents a unique component score. Component scores were graphed as percentages, e.g., a Total Fruits score of 4/5 was graphed as 80%. A perfect HEI-2015 score (100% for each component) would be displayed as a line around the border of the radar graph. All descriptive analyses were conducted with IBM SPSS Statistics version 23 software (IBM Corp., Armonk, NY, USA), all statistical modeling was conducted with SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA), and radar graphs were created using Microsoft Excel 2013 (Microsoft Corp, Redmond, WA, USA). All p values were 2-sided, and $p < 0.05$ was defined as statistically significant.

3.4 Results

3.4.1 Participant Characteristics

A total of 51,442 mortality cases were documented (26,376 men and 25,066 women) over 17–22 years of follow-up (Table 3.2). Of these cases, 17,662 deaths were from CVD (9130 men and 8532 women) and 14,778 were from cancer (7812 men and 6966 women). Compared to men and women in quintile 1 (lowest diet quality), participants in quintile 5 (highest diet quality) on average were older at the time they completed the Qx1, had a lower BMI, lower energy intake, and more weekly hours of moderate to vigorous physical activity. Quintile 5

also contained a larger proportion of people with diabetes, those who never smoked, and those who graduated from college, compared to quintile 1. Among both men and women, there were higher proportions of Japanese American, Latino, and Native Hawaiian participants in quintile 1 compared to quintile 5, and a higher proportion of white and African American participants in quintile 5 compared to quintile 1. There was a lower proportion of married women in quintile 5 than in quintile 1, and a higher proportion of married men in quintile 5 than in quintile 1. A higher proportion of women in quintile 5 were users of hormone-replacement therapy, compared to all other quintiles. Mean HEI-2015 scores by sex and ethnic group are in Appendix G.

Table 3.2 Descriptive characteristics of participants (n = 156,804) in the Multiethnic Cohort by quintiles of Healthy Eating Index-2015 (HEI-2015) scores.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Men (*n* = 70,170)					
HEI-2015 scores, range	17.9–56.1	56.2–62.1	62.2–67.5	67.6–74.0	74.1–98.7
Mean HEI-2015 score ***	50.7	59.4	64.9	70.7	79.6
N	14,034	14,034	14,035	14,033	14,034
Mortality, *n* cases	5003	5177	5321	5355	5520
Cardiovascular disease	1708	1740	1864	1894	1924
Cancer	1566	1598	1572	1561	1515
Age at time of death, years [1]	74.4 ± 9.6	75.9 ± 9.4	77.0 ± 9.2	77.9 ± 9.1	79.3 ± 8.6
Age at time of questionnaire, years [1,***]	56.8 ± 8.6	58.3 ± 8.7	59.4 ± 8.7	60.0 ± 8.7	61.1 ± 8.6
Ethnicity, % of row					
Japanese American (*n* = 21,239)	24.1	21.5	20.0	17.8	16.6
Latino (*n* = 17,595)	20.7	23.1	22.8	19.8	13.7
White (*n* = 17,330)	14.9	16.3	18.0	23.0	28.0
African American (*n* = 9014)	15.1	17.0	19.2	21.7	26.9
Native Hawaiian (*n* = 4992)	27.0	20.9	18.7	17.2	16.3
Body mass index (kg/m^2) [1,***]	26.9 ± 4.5	26.9 ± 4.3	26.8 ± 4.2	26.6 ± 4.1	26.1 ± 3.8
Energy intake, kcal [1,***]	2479 ± 1158	2552 ± 1220	2524 ± 1181	2448 ± 1107	2256 ± 978
Physical activity, h/week [1,2,***]	1.2 ± 1.5	1.3 ± 1.6	1.4 ± 1.5	1.4 ± 1.5	1.5 ± 1.5
History of diabetes, % with diabetes ***	8.4	10.0	11.4	11.7	12.5
Smoking, % who never smoked ***	24.3	28.0	30.6	33.8	37.7
Education, % graduated from college ***	23.9	26.2	28.6	33.3	38.5
Marital status, % married	74.5	76.3	77.7	76.8	75.2
Women (*n* = 86,634)					
HEI-2015 scores, range	23.5–59.8	59.9–66.3	66.4–71.8	71.9–78.0	78.1–99.8
Mean HEI-2015 score ***	53.8	63.3	69.2	74.9	83.0
N	17,327	17,326	17,328	17,327	17,326
Mortality, *n* cases	4603	4809	5020	5119	5515
Cardiovascular disease	1493	1637	1747	1782	1873
Cancer	1398	1365	1385	1353	1465
Age at time of death, years	75.1 ± 9.9	77.3 ± 9.6	78.3 ± 9.1	79.5 ± 9.1	80.4 ± 8.6

Age at time of questionnaire, years ***	56.4 ± 8.6	58.2 ± 8.7	59.3 ± 8.7	60.1 ± 8.8	61.5 ± 8.5
Ethnicity, % of row					
Japanese American (*n* = 24,785)	21.1	21.5	20.1	19.0	18.3
White (*n* = 20,653)	15.8	16.6	19.7	22.9	25.0
Latina (*n* = 18,756)	25.4	24.1	21.2	17.0	12.4
African American (*n* = 16,072)	15.0	17.0	19.3	22.3	26.5
Native Hawaiian (*n* = 6368)	26.1	20.8	18.8	17.8	16.5
Body mass index (kg/m^2) ***	27.1 ± 6.2	26.7 ± 5.8	26.5 ± 5.6	26.1 ± 5.4	25.5 ± 5.2
Energy intake, kcal ***	2052 ± 1068	2038 ± 1023	2003 ± 967	1956 ± 915	1865 ± 817
Physical activity, h/week [2,]***	1.0 ± 1.2	1.0 ± 1.3	1.1 ± 1.3	1.2 ± 1.3	1.3 ± 1.3
History of diabetes, % with diabetes ***	8.2	9.3	9.8	9.5	10.1
Smoking, % never smoked ***	50.5	55.8	56.5	57.9	58.7
Education, % graduated from college ***	18.7	21.3	23.9	27.4	31.3
Marital status, % married *	59.1	60.9	60.5	59.4	57.6
Hormone replacement therapy, % users ***	37.4	42.7	46.1	49.2	53.1

*** p value < 0.001 for independent sample t-test between quintile 1 and quintile 5 for quantitative variables and test of proportions for discrete variables collected at baseline. [1] Mean ± SD (all such values). * p value < 0.05 between quintile 1 and quintile 5, for test of proportions for discrete variables collected at baseline. [2] Represents self-reported weekly hours of moderate to vigorous physical activity.

3.4.2 Mortality Analysis

For men and women, participants in quintile 5 were at lower risk of all-cause, CVD, and cancer mortality compared to participants in quintile 1 (Table 3.3). For men, the quintile 1: quintile 5 HRs (95% CIs) for all-cause, CVD, and cancer for were 0.79 (0.76, 0.82), 0.76 (0.71, 0.82), and 0.80 (0.75, 0.87), respectively. For women, the HRs (95% CIs) were 0.79 (0.76, 0.82), 0.75 (0.70, 0.81), and 0.84 (0.78, 0.91), respectively. With every increase across quintiles of diet quality, there was a decrease or no change in risk of death from all-cause, CVD, and cancer for both men and women. The change in risk from all-cause and CVD mortality between quintile 1 and quintile 5 was similar for men and women. For cancer mortality, quintile 1: quintile 5 HR results supported a 20% reduction in risk of death for men compared to women, who had a 16% lower risk.

In men, when stratified by ethnicity, a protective effect was seen for quintile 1: quintile 5 for all-cause, CVD, and cancer mortality among the white, African American, and Japanese American groups, with all HR ≤ 0.83 (Appendix E). Latino men in quintile 1: quintile 5 had a reduced risk of all-cause and cancer mortality with HRs of 0.88 and 0.79, respectively, and a null association for CVD mortality. For Native Hawaiian men there was a null association for all mortality outcomes and for the tests for trend. In women, when stratified by ethnicity, a protective effect for all-cause, CVD, and cancer mortality was observed for white women in quintile 1: quintile 5 with HRs of 0.66, 0.63, and 0.71, respectively (Appendix F). African American and Japanese American women in quintile 1: quintile 5 had a reduced risk of all-cause and CVD mortality, with HR ≤ 0.72 for African American women and HR ≤ 0.87 for Japanese American women. African American and Japanese American women in quintile 1: quintile 5 had a null association for cancer mortality. Latino women in quintile 1: quintile 5 had a reduced risk of all-cause and cancer mortality, with HR ≤ 0.92, and a null association for CVD morality. There was a null association for all mortality outcomes for Native Hawaiian women and for the tests for trend. CVD mortality among Latino women, and cancer mortality among the African American and Japanese American women did not have significant tests for trend. The test for trend was statistically significant for the majority of the relationships tested.

Removing any one of the 13 components from the HEI-2015 score did not substantially change the association of the index with mortality outcomes for both men and women (Figure 3.1 and Appendix B-D). Removing the Refined Grains component (component 10) changed the quintile 1: quintile 5 HR for men from 0.79 (0.76, 0.82) to 0.75 (0.72, 0.78) for all-cause mortality, 0.76 (0.71, 0.82) to 0.73 (0.68, 0.78) for CVD mortality, and 0.80 (0.75, 0.87) to 0.74 (0.68, 0.79) for cancer mortality. Repeating the same concept with the Saturated Fats component (component 13) changed the quintile 1: quintile 5 HR for men from 0.79 (0.76, 0.82) to 0.82 (0.78, 0.85) for all-cause mortality, 0.76 (0.71, 0.82) to 0.80 (0.74, 0.85) for CVD mortality, and 0.80 (0.75, 0.87) to 0.84 (0.78, 0.91) for cancer mortality. These were the largest changes seen and yet these HRs were still relatively close. When the HEI-2015 scoring standards were applied to the MEC sample with fewer mortality cases from the follow-up period of the HEI-2010 mortality analysis [19], similar associations with mortality risk were observed. The quintile 1: quintile 5 HRs were 0.78 (0.75, 0.82), 0.78 (0.72, 0.84), and 0.80 (0.73, 0.87) for all-cause, CVD, and cancer mortality, respectively, for men and 0.79 (0.75, 0.84), 0.77 (0.71, 0.85), and 0.89 (0.81, 0.97), respectively, for women.

Table 3.3 Hazard ratios (HR) (95% confidence intervals (CI)) for all-cause, cardiovascular disease (CVD), and cancer mortality according to quintiles of Healthy Eating Index-2015 (HEI-2015) scores in men (n = 70,170) and women (n = 86,634) in the Multiethnic Cohort [1].

HEI-2015 Category	*n*	Any Deaths *n*	Person-Years of Follow-Up	All-Cause Mortality [1] HR (95% CI)	CVD Deaths *n*	CVD Mortality [1] HR (95% CI)	Cancer Deaths *n*	Cancer Mortality [1] HR (95% CI)
Men [2,3]								
Quintile 1	14,034	5003	252,098	1.00	1708	1.00	1566	1.00
Quintile 2	14,034	5177	250,512	0.93 (0.90, 0.97)	1740	0.90 (0.84, 0.96)	1598	0.97 (0.90, 1.04)
Quintile 3	14,035	5321	250,072	0.89 (0.85, 0.92)	1864	0.88 (0.82, 0.94)	1572	0.91 (0.85, 0.98)
Quintile 4	14,033	5355	250,974	0.85 (0.81, 0.88)	1894	0.84 (0.78, 0.90)	1561	0.88 (0.82, 0.95)
Quintile 5	14,034	5520	252,489	0.79 (0.76, 0.82)	1924	0.76 (0.71, 0.82)	1515	0.80 (0.75, 0.87)
Women [3,4]								
Quintile 1	17,327	4603	327,551	1.00	1493	1.00	1398	1.00
Quintile 2	17,326	4809	327,362	0.92 (0.89, 0.96)	1637	0.93 (0.87, 1.00)	1365	0.93 (0.86, 1.00)
Quintile 3	17,328	5020	325,938	0.87 (0.84, 0.91)	1747	0.88 (0.82, 0.95)	1385	0.90 (0.83, 0.97)
Quintile 4	17,327	5119	326,802	0.82 (0.79, 0.86)	1782	0.83 (0.77, 0.89)	1353	0.84 (0.78, 0.91)
Quintile 5	17,326	5515	325,836	0.79 (0.76, 0.82)	1873	0.75 (0.70, 0.81)	1465	0.84 (0.78, 0.91)

[1] p-trend < 0.0001 for all models. [2] Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, ethnicity, education, marital status, smoking, weekly hours of moderate to vigorous physical activity, and alcohol intake. [3] Quintile 1 is lowest score and quintile 5 is highest score, HEI ranges shown in Table 3.2 [4] Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, ethnicity, education, marital status, smoking, physical activity, hormone replacement therapy, and alcohol intake.

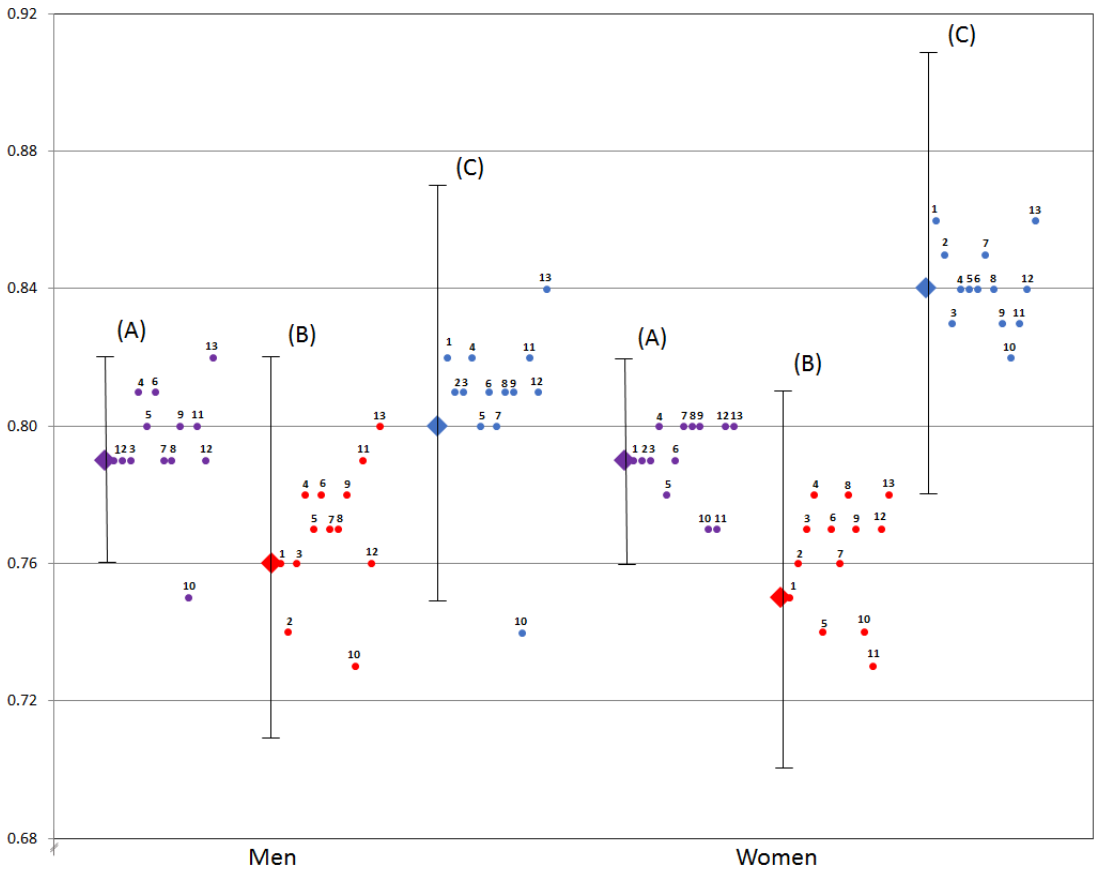

Figure 3.1 Quintile 1: quintile 5 hazard ratios (HR) and 95% confidence intervals (CI) for all-cause, cardiovascular disease (CVD) and cancer mortality for Healthy Eating Index-2015 (HEI-2015) scores with one component removed for men and women in the Multiethnic Cohort. Diamond shapes represent HR for mortality by (A) all-cause (purple), (B) CVD (red) and (C) cancer (blue) for men and women, as per results shown in Table 3.3 Smaller dots represent HR for HEI-2015 with one component removed. When excluded, the component is labeled as: (1) Total Fruits, (2) Whole Fruits, (3) Total Vegetables, (4) Greens and Beans, (5) Whole Grains, (6) Dairy, (7) Total Protein Foods, (8) Seafood and Plant Proteins, (9) Fatty Acids, (10) Refined Grains, (11) Sodium, (12) Added Sugars, (13) Saturated Fats. All models were adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, ethnicity, education, marital status, smoking, weekly hours of moderate to vigorous physical activity, and alcohol intake. All models for women were also adjusted for hormone replacement therapy.

3.4.3 Radar Graphs

Figure 3.2 displays radar graphs which can be used to visualize the range of intakes among the components. A perfect HEI-2015 total score (100% for each component) would be displayed as a line around the border of the radar graph. The median component scores for men in quintile 1 (the lowest quality diet group) were 50% or less for the adequacy components of Total Fruits, Whole Fruits, Greens and Beans, Whole Grains, and Dairy, as well as for the moderation components of Fatty Acids, Sodium, and Refined Grains (Figure

3.2A). For Total Vegetables (an adequacy component) and Saturated Fats (a moderation component), the median component scores in quintile 1 for men were between 50% and 80%. Seafood and Plant Proteins, and Total Protein Foods (adequacy components), and Added Sugars (a moderation component) were all above 80%. The lowest median component scores for men in quintile 5 were Dairy (41%), Fatty Acids (78%) and Sodium (59%). All other median component scores for men in quintile 5 were over 84%. The median component scores for women in quintile 1 were 50% or less for Total Fruits, Whole Grains, Dairy, Fatty Acids, Refined Grains, and Sodium (Figure 3.2B). The median component scores in quintile 1 for women were between 50% and 80% for Whole Fruits, Total Vegetables, Greens and Beans, and Saturated Fats, and over 80% for Total Protein Foods, Seafood and Plant Proteins, and Added Sugars. The lowest median component scores for women in quintile 5 were Dairy (51%), Fatty Acids (79%), and Sodium (63%). All other median component scores for women in quintile 5 were over 95%. Patterns of the median component scores were similar for men and women in quintile 1 and in quintile 5, e.g., Total Protein Foods scored the highest and Dairy scored the lowest for men and women in both quintiles. Women had higher median scores for each component, with the exception of men having higher median component scores for Seafood and Plant Proteins, Fatty Acids, Sodium, and Saturated Fats in quintile 1. Comparing the total HEI-2015 median scores between the sexes for quintile 1 and for quintile 5, women had higher median total HEI-2015 scores than men.

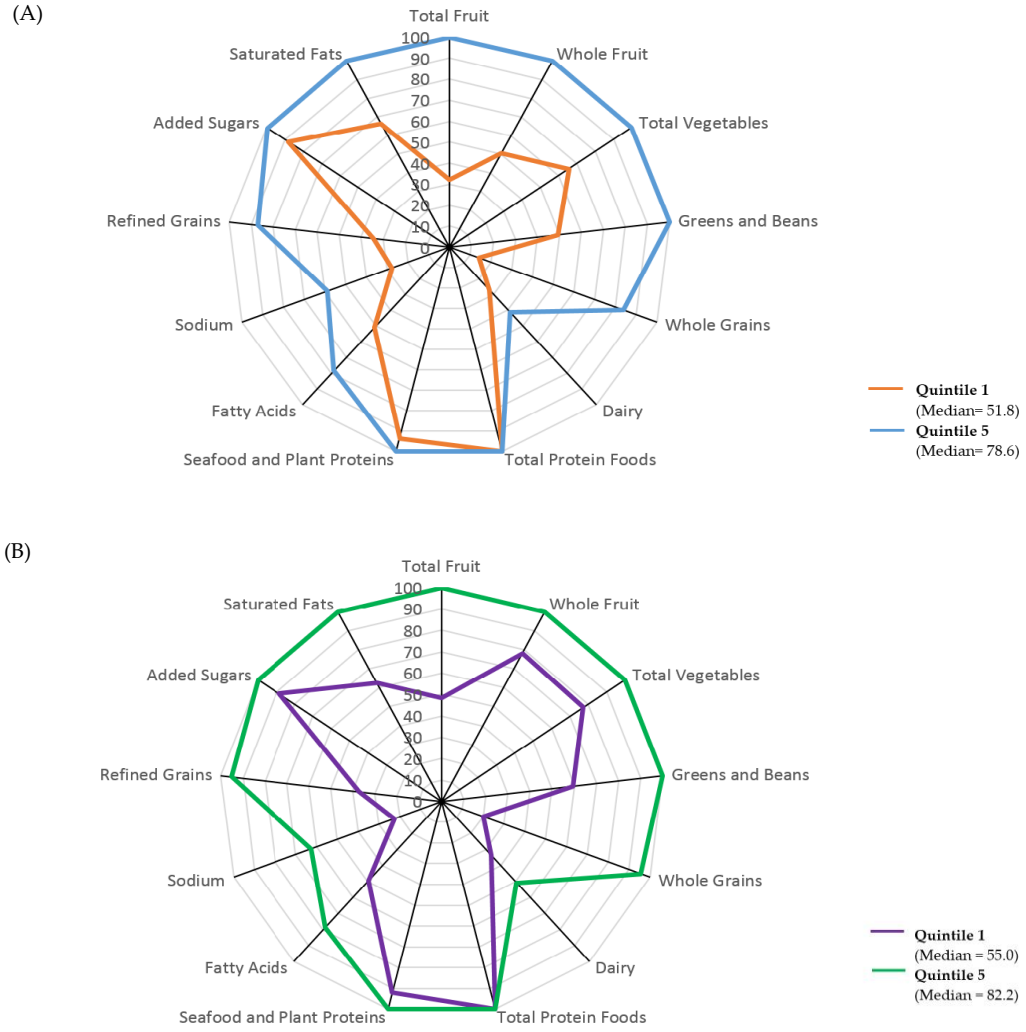

Figure 3.2 Total median scores and radar graphs of median component scores for (A) men and (B) women in Healthy Eating Index-2015 (HEI-2015) quintile 1 and quintile 5 in the Multiethnic Cohort.

3.5 Discussion

Comparing those with the lowest quality diets to those with the highest quality, the reduction in risk of mortality from all-cause, CVD, and cancer was 21%, 24%, and 20%, respectively, for men and 21%, 25%, and 16%, respectively, for women. In the HEI-2010 mortality analysis with the MEC, the reduction in the risk of mortality from all-cause, CVD, and cancer was 25%, 26%, and 24%, respectively, for men, and 21%, 23%, and 11%, respectively, for women [19]. Therefore, HRs have slightly improved for women and marginally lowered for men between the HEI-2015 and HEI-2010 mortality analyses with the MEC. When the HEI-2015 scoring standards were applied to the MEC sample with fewer mortality cases, from the follow-up period of the HEI-2010 mortality analysis, the HR results were also very similar. The reduction in risk of mortality from all-cause, CVD, and cancer was 22%, 22%, and 20%, respectively, for men and 21%, 23%, and 11%, respectively, for

women. For the DPMP, standardized mortality assessments were also conducted with the HEI-2010 and the WHI-OS, and AARP cohorts. The HEI-2010 mortality analysis with the WHI-OS was conducted with 63,115 US women, of whom 83% identified as white [21,30]. The results of this study showed a reduction in risk between quintile 1: quintile 5, with HRs of 24%, 22%, and 23% for all-cause, CVD, and cancer mortality, respectively. The HEI-2010 mortality analysis for the AARP contained 242,321 men and 182,342 women from six US states and over 90% of participants identified as white [17,31]. The same mortality analysis applied to the AARP showed a reduction in risk of 22%, 15%, and 24% for all-cause, CVD, and cancer mortality, respectively, for men and 23%, 21%, and 18%, respectively, for women. The results from the HEI-2015 mortality analysis with the MEC and the HEI-2010 mortality analysis with the WHI-OS and AARP are very similar, more so than the mortality results from the HEI-2010 analyses with the MEC. For example, the reduction in risk of cancer mortality for women in the MEC, WHI-OS, and AARP were 11%, 23%, and 18%, respectively, using the HEI-2010. The reduction in risk of cancer mortality for women in the MEC changed to 16% in the HEI-2015 analysis. A recent meta-analysis on the association between the HEI-2005/HEI 2010, AHEI, and DASH and health outcomes for both men and women had similar findings to this HEI-2015 analysis with the MEC [32]. Consistency between the HEI-2010 analyses and this HEI-2015 analysis reinforces the use of HEI as an assessment of diet quality.

The analysis that removed one component at a time did not change the protective association of the remaining HEI components. Therefore, no one HEI component made an independent significant contribution to the total score (Figure 3.1). The Saturated Fat component did distinguish itself, as its removal changed the HRs slightly towards the null for all three mortality outcomes among men only. Previous versions of the HEI included Saturated Fat as part of the empty calories component comprised of solid fat, added sugars, and alcohol [3]. The HEI-2015 offers the first opportunity to evaluate the Added Sugars and Saturated Fat components independently, however alcohol is now part of total energy intake. Removal of the Added Sugars component had no influence on moving the hazard ratios. On the other hand, the component whose removal consistently changed the HRs away from the null was Refined Grains for all-cause mortality, CVD mortality, and cancer mortality among men only, although this shift was minor and did not change the overall results. The by-component models using HEI-2010 among the members of the AARP cohort reported the unexpected finding of an increase in risk for all-cause mortality among men and women with higher scores for the Refined Grain component (indicating lower consumption) [16]. Future analysis might consider reconciling these observations across the HEI-2010 and HEI-2015 and the cohorts involved in the DPMP. These results support and reinforce the multidimensionality of the HEI and the representation of diet quality using a wide array of components.

Higher diet quality was associated with improved mortality outcomes in this analysis among a multiethnic population of men and women. All of the HEI-2015 components contributed to the association of diet quality and mortality. Given this, dietary components needing improvement for people with the lowest quality diets could be emphasized in public health messages. The components with the largest differences in median scores between quintile 1 and quintile 5 were identified as Total Fruits, Whole Fruits, Greens and Beans, Whole Grains, and Refined Grains for men and Total Fruits, Whole Grains, and Refined Grains for women (Figure 3.2). The results of the present analysis suggest increasing the intake of foods that fall into these components may improve mortality outcomes for

people with the lowest quality diets. Data from the 2007-2010 National Health and Nutrition Examination Survey (NHANES) reported that men and women 31 years and older in the US do not meet the requirements for fruits, vegetables, and whole grains and exceed the recommended intake of refined grains [4,33]. The message on increasing the intake of fruits, vegetables, and whole grains to improve health outcomes is consistent with results from both the MEC and NHANES [4,33].

The components with the lowest median scores were the same for people in quintile 1 and quintile 5. These components were Dairy, Fatty Acids, and Sodium, with median scores of less than 50%. Improving scores for Dairy, Fatty Acids, and Sodium components may help to improve mortality outcomes for people with the lowest quality diets. The current mortality analysis does not provide evidence on whether increasing Dairy, Fatty Acids, and Sodium component scores for people with the highest quality diets will offer any additional protection. The DGA reports, on average, that adults in the US are not achieving their recommended intakes of dairy and oils, and average intakes of saturated fats and sodium are met or exceeded [4]. The MEC results and the DGAs support evidence that people with low quality diets should increase their intakes of these foods to improve health outcomes [4,33]. The current dietary guidelines also promote replacing SFAs with PUFAs to reduce CVD-related deaths and decreasing sodium intake to reduce CVD events [4]. Based on this evidence from the DGAs and the MEC, people with the highest quality diets may have improved mortality outcomes if they meet recommended intakes of SFAs, PUFAs, and sodium.

The median component scores for men and women in the MEC in quintile 1 and quintile 5 were at 100% (a perfect score) for the Total Protein Foods component. Similarly, results from NHANES 2007–2010 support that mean intakes of meat, poultry, and eggs for adults 31 years and older are at recommended levels for women and at or above recommended levels for men [4,33]. The standard for a perfect score for Total Protein Foods is ≥2.5 oz per 1000 kcal per day. There is no upper limit for Total Protein Foods using this scoring standard; therefore, we do not know if consuming more than 2.5 oz of Total Protein Foods per 1000 kcal per day further improves or worsens mortality outcomes. Also, we do not know if consuming Total Protein Foods in excess replaces intake of foods found in the other 12 components, which would lower these component scores. Having no upper limit for component scoring standards may be a limitation of the HEI.

The median component scores for quintile 1 and quintile 5 for Added Sugars for men and women in the MEC were each above 88%. In comparison, the average intake of added sugar for adults in NHANES were all above the recommended maximum limit [4,33]. Previous research on the MEC found that Japanese Americans had the greatest percentage of people who met the DGA recommendations for added sugars [34,35]. The MEC has a large proportion of Japanese Americans (26.4%), which may explain why median component scores for Added Sugars indicate a low intake in the MEC compared to excessive average intakes in NHANES. For the Seafood and Plant Proteins component, the median scores among the MEC men and women in both the 1st and 5th quintiles were above 80%. Results reported from NHANES 2007-2010 indicated intakes of nuts, seeds, and soy products were at or above recommended intakes among adults, whereas seafood intakes were below recommendations [4,33]. Previous research shows that Native Hawaiians and Japanese Americans in the MEC have more servings of fish per day than other ethnic groups [34,35]. These two ethnic groups make up 1/3 of the MEC sample; therefore, their seafood

intake may contribute to the median component scores of over 80% for Seafood and Plant Proteins.

The overall mean HEI-2015 score among men and women in the MEC, as estimated using the FFQ, was 65 and 69, respectively. Among men, Native Hawaiian men had the lowest score at 63 compared to African American and white men, with scores of 67. For women, the range was 71 among African American and white women to 67 among Native Hawaiian women. At the time of this paper, no published information about HEI-2015 scores among adults or children had been published. For any comparison, HEI-2015 scores derived from a FFQ would be preferable, as was done by Liese et al. [15]. Although the mean scores by ethnic group were almost all statistically significantly different, the range of scores was small, i.e., four points for both men and women. An examination of component scores between ethnic groups to further explore variation in dietary exposures is warranted.

Identifying the characteristics of people with the lowest quality diets may help to further tailor nutrition education messages. Comparing the results across the WHI-OS, AARP, and MEC cohorts, college graduates were more likely to be classified as having a higher quality diet based on HEI-2010 [16,21]. In the AARP and MEC cohorts, women had slightly higher diet quality scores than men [16]. For both men and women in the MEC, a higher percentage of Japanese Americans, Native Hawaiians, and Latinos were in quintile 1 and a higher percentage of whites and African Americans were in quintile 5. The WHI-OS cohort is comprised of women and similar to the women in the MEC cohort, there was a higher percentage of whites in quintile 5 compared to quintile 1 and a higher percentage of Hispanic women in quintile 1 compared to quintile 5 [21]. In the WHI-OS, a greater percentage of Black women were in quintile 1 compared to quintile 5, which is in contrast to the MEC, where a larger proportion of Black women were in quintile 5 [21]. Thus, the quality of diet within any one group may vary by geographic area.

Of note, the highest versus the lowest HEI-2015 scores were consistently more protective for white and African Americans. The development of the HEI is guided by evidence-based research, and nutrition research is dominated by studies conducted among white and African American participants [36–39]. This may account for why the HEI-2015 performs better for white and African Americans. In this analysis, Native Hawaiian men and women had a null association between HEI-2015 quintile 1: quintile 5 and all-cause, CVD, and cancer mortality. Native Hawaiians have the lowest sample size compared to all other ethnic groups in the MEC. Therefore, the power for the analyses of diet quality and mortality outcomes in Native Hawaiians may not be large enough to draw significant findings. Latino men and women also had null associations between HEI-2015 quintile 1: quintile 5 and CVD mortality. Latinos in the US have the lowest rate of CVD compared to other ethnic groups [40]. These rates are mimicked in this current analysis, with Latino men and women making up 25% and 22% of this MEC sample, respectively, but having the second lowest rate of CVD mortality behind Native Hawaiians. Therefore, the relatively lower rate of CVD mortality in Latino men and women may be contributing to the null association between diet quality and CVD mortality. The associations between the HEI-2015 and mortality outcomes by ethnic group in the MEC are similar to those found in the HEI-2010 mortality analysis with the MEC [19].

A limitation of this study was the use of a food frequency questionnaire (FFQ) to collect dietary information at baseline, which could introduce bias [22]. However, this QFFQ was validated and calibrated in each ethnic-sex group and the correlations between the QFFQ and 24-hour dietary recalls were 0.55–0.74 for energy adjusted nutrients [22]. Another

limitation was dietary data only being assessed once at baseline; therefore, this analysis was not able to capture the influence of dietary changes on mortality outcomes. In addition, all demographic and anthropometric variables were self-reported, and we cannot rule out whether other factors not measured and controlled for, could have affected mortality outcomes; e.g., access to health care. Participants in the MEC were recruited from Hawaii and LA; therefore, results of this study may not be generalizable outside of these areas. Lastly, measurement error is an important consideration relevant to all self-reported behavioral variables. The simple models used to examine predictive validity do not address measurement error; however, efforts are underway to do so for future analyses.

The strengths of this study include the use of a large multiethnic sample that was followed prospectively for over 17 years and the use of a comprehensive QFFQ that was designed to capture ethnic specific foods, allowing for this multiethnic comparison. In addition, covariate data at baseline were collected for almost every participant, permitting the adjustment for multiple, salient risk factors. This study also applied the same standardized regression analysis previously used in diet quality and mortality analysis by the DPMP. Using this standardized approach allows comparisons to be made between the present study and previous and future DPMP analyses of dietary indices and mortality outcomes. For example, once finalized, comparisons can be made between the MEC, the WHI-OS and the AARP mortality analysis with the HEI-2015.

3.6 Conclusions

In summary, people in the MEC with higher HEI-2015 scores had a reduction in risk of all-cause, CVD, and cancer mortality. Updates to component scoring between the HEI-2010 and HEI-2015 do not appear to have affected the balance of the scoring system, and mortality analysis results were robust between studies that used either index. Increasing intake of whole fruits, vegetables, whole grains, MUFA, PUFA and reducing intake of refined grains, sodium, and saturated fats may improve dietary patterns and mortality outcomes for people with the poorest quality diets. Improving intake as a whole versus any single food group appears to be most beneficial in reducing risk for mortality. The HEI-2015 is a useful means by which to measure diet quality.

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Conflicts of Interest: The authors declare no conflict of interest.

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CHAPTER 4. EFFECTS OF INTERMITTENT ENERGY RESTRICTION COMBINED WITH A MEDITERRANEAN DIET ON REDUCING VISCERAL ADIPOSITY: A RANDOMIZED ACTIVE COMPARATOR PILOT STUDY

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4.1 Abstract

Intermittent energy restriction combined with a Mediterranean diet (IER+MED) has shown promise to reduce body fat and insulin resistance. In the Multiethnic Cohort Adiposity Phenotype Study, Japanese Americans had the highest visceral adipose tissue (VAT) when adjusting for total adiposity. We conducted this pilot study to demonstrate feasibility and explore efficacy of following IER+MED for 12 weeks to reduce VAT among East Asians in Hawaii. Sixty volunteers (aged 35–55, BMI 25–40 kg/m^2, VAT ≥ 90 cm^2 for men and ≥ 80 cm^2 for women) were randomized to IER+MED (two consecutive days with 70% energy restriction and 5 days euenergetic MED) or an active comparator (euenergetic Dietary Approaches to Stop Hypertension (DASH) diet). Participants and clinic staff (except dietitians) were blinded to group assignments. IER+MED had significantly larger reductions in DXA-measured VAT and total fat mass (−22.6 ± 3.6 cm^2 and −3.3 ± 0.4 kg, respectively) vs. DASH (−10.7 ± 3.5 cm^2 and −1.6 ± 0.4 kg) (p = 0.02 and p = 0.005). However, after adjusting for total fat mass, change in VAT was not statistically different between groups; whereas, improvement in alanine transaminase remained significantly greater for IER+MED vs. DASH (−16.2 ± 3.8 U/L vs.–4.0 ± 3.6 U/L, respectively, p = 0.02). Attrition rate was 10%, and participants adhered well to study prescriptions with no reported major adverse effect. Results demonstrate IER+MED is acceptable, lowers visceral and total adiposity among East Asian Americans, and may improve liver function more effectively than a healthful diet pattern. ClinicalTrials.gov Identifier: NCT03639350.

4.2 Introduction

Excess adiposity contributes to an increased risk of cardiovascular disease, type 2 diabetes, and at least 13 cancers, including postmenopausal breast, endometrium, liver, gallbladder, pancreas, thyroid, kidney and colon cancer [1,2]. Visceral adiposity more so than subcutaneous adiposity is associated with the cardiovascular and metabolic consequences of obesity [3,4]. Higher visceral adipose tissue (VAT) levels result in increased circulating proinflammatory cytokines and adipokines, and a decrease in protective adipokines [4–8]. Also, non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) have emerged as common liver diseases due to excess adiposity and are associated with type 2 diabetes, metabolic syndrome, and liver cancer [9].

Asians and Asian Americans are at a higher metabolic risk from excess adiposity compared to whites and other racial/ethnic populations [10]. In the Multiethnic Cohort Adiposity Phenotype Study (MEC-APS), conducted in Hawaii and California, we observed Japanese Americans preferentially store excess fat as VAT over subcutaneous adipose tissue (SAT) and also have higher levels of liver fat compared to participants of African American, Latino, Native Hawaiian or white ancestry after adjusting for total adiposity [11]. Consistent with this observation, among 23,830 men in the MEC over the median follow-up of 16.6 years, Japanese Americans showed a stronger association of higher body mass index (BMI) with the risk of hepatocellular carcinoma (HCC; relative risk (RR) for a 5 kg/m^2 increase in BMI = 1.77) compared to African American, Latino, Native Hawaiian, and white men (RRs ranging 0.78–1.34) [12]. Other studies comparing Asians or Asian Americans to whites also found a higher prevalence of visceral obesity, NAFLD and metabolic syndrome [13,14], suggesting this group may benefit from an intervention aimed at reducing adiposity, especially VAT.

While energy restriction is the most common strategy for weight loss and visceral fat reduction [15], long-term adherence to continuous energy restriction (CER) is known to be difficult [16], and intermittent energy restriction (IER) has emerged as a promising alternative to CER [17]. IER includes periods of marked energy restriction (typically 60–75% below estimated energy requirements) on at least one day but no more than six days per week, interspersed with periods of normal or ad libitum energy intake [17–21]. In particular, Harvie et al. suggested combining two consecutive days of IER with five days of a Mediterranean (MED) type diet to promote satiety and high-quality nutrition [17,22]. The MED diet is primarily a plant-based diet rich in olive oil, olives, fruits, vegetables, whole grains, legumes and nuts with moderate amounts of dairy products (principally cheese and yogurt), fish, poultry, red wine, and limited amounts of red meat [23–25]. Adherence to a MED diet was also promoted for the management of NAFLD in joint clinical practice guidelines issued by the European Associations for the Study of Liver (EASL), Diabetes (EASD) and Obesity (EASO) [26]. These guidelines also recommended patients with NAFLD restrict energy intake, lose weight if overweight or obese, and incorporate aerobic exercise or resistance training [26]. Consistently, in the MEC-APS, we observed following a high-quality diet, e.g., a high MED index score, was inversely associated with adiposity, including VAT and liver fat as assessed by magnetic resonance imaging (MRI)[27]. Thus, adopting IER combined with a MED diet on the non-restricted days may help to reduce VAT, and assist with controlling other ectopic fat stores.

The primary aim of the present study was to finalize and implement a protocol for an intermittent energy restriction (IER) intervention to evaluate the effectiveness of a culturally

adapted IER and MED combined diet (IER+MED) to reduce VAT among East Asian Americans. Secondary aims were to evaluate study retention and protocol adherence, and changes in total adiposity and metabolic risk biomarkers. East Asian women and men were also prioritized for this study as their traditional and acculturated East Asian diets are dissimilar compared to the IER+MED diet. Therefore, limiting enrollment to men and women of East Asian ancestry for participation in this pilot study allowed full attention to be directed to adapting their diets.

4.3 Materials and Methods

4.3.1 Study Design and Participants

The Healthy Diet and Lifestyle Study (HDLS) pilot was a two-arm randomized trial conducted between September 2016 and October 2017 at the University of Hawaii Cancer Center (UHCC) to demonstrate the feasibility of a nutritional intervention aimed at reducing visceral adiposity in East Asian middle-aged adults. This study included two clinic visits before the intervention (an eligibility visit and a baseline visit approximately one week apart (1.25 ± 1.2 weeks)), a 12 week intervention phase, a final clinic visit at Week 12, and a 6-month post-intervention telephone interview. Participants who responded to the study promotions, were first screened over the telephone to assess the inclusion criteria of East Asian ancestry (Japanese, Chinese, or Korean), residence in Honolulu County, body mass index (BMI) between 25 and 40 kg/m^2, ages 35 to 55 years, and no serious health issues. Exclusion criteria included; smoking tobacco products or marijuana in the past two years, taking thyroid medication, prescription medication or insulin for type 1 or type 2 diabetes, anti-estrogen medication (women), anti-androgen medication (men), substantial change of weight of more than ± 10 kg in the past six months, following a special diet (e.g., vegan), or alcohol intake >15 drinks per week for men or >10 drinks per week for women. Ethnicity was self-reported and at least two biological grandparents of pure East Asian ancestry were required. Those screened as eligible were scheduled for an eligibility visit, which consisted of a fasting blood draw, anthropometric measurements, questionnaires (characteristics, medical history, medication list, physical activity), a whole-body dual energy X-ray absorptiometry (DXA) scan, and training participants how to complete a mobile food record (mFR™) [28–31] to capture images with their mobile device of foods/beverages before and after each eating occasion over 4 contiguous days. Final eligibility was determined based on general good health, normal blood count and biochemistry profile, and DXA-derived visceral fat area at L4-L5 intervertebral region ≥ 90 cm^2 for men or ≥ 80 cm^2 for women to target at-risk individuals for visceral obesity based on VAT distribution in the MEC-APS study [11]. The baseline clinic visit involved randomizing participants into the IER+MED group or the active comparator DASH group, education of diet and physical activity prescriptions, and reviewing information from mFRs™collected between the eligibility and baseline visits. During the final clinic visit, measurements taken at baseline were repeated.

The enrollment goal was to recruit 70 persons to achieve a final sample of 50 persons to account for an attrition rate of ~23%, as reported in past studies [22]. Participants were recruited through advertisements in local newspapers, on radio stations, television news, social media, and email list-servs, and through distribution of brochures and flyers. A total of 820 people responded to the study promotions and of these, 760 people were excluded due to not meeting the eligibility criteria or declining to participate (Figure 4.1). As

reimbursement for time and travel, each participant received a $50 gift card at the eligibility visit, $50 at the baseline clinic visit, and $50 at the final clinic visit, totaling $150 in gift cards to a state-wide supermarket chain. Participants were provided their whole-body DXA, BMI, and blood biochemistry panel results after the baseline and final clinic visits. All study procedures were approved by the University of Hawaii Institutional Review Board and written informed consent was obtained from all study participants.

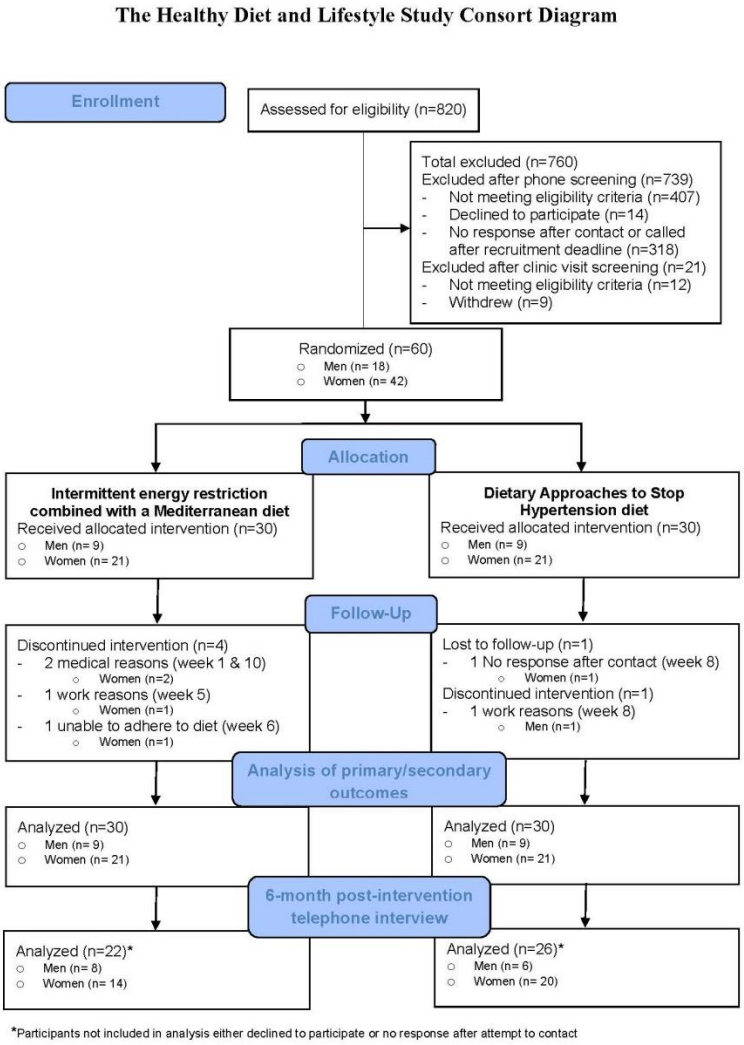

Figure 4.1 Consort diagram.

4.3.2 Randomization and Masking

Randomization was implemented within strata defined by sex and VAT levels (above or below 150 cm^2) and was blocked to ensure balance in assignment over the course of the study [32,33]. Stratified blocked randomization schedules were created by biostatisticians not involved in the intervention [33]. The assignments were printed and placed in opaque sealed envelopes with consecutive numbering and unique colors by strata. During the baseline clinic visit, research dietitians provided the participants with the next four consecutive envelopes in the appropriate stratum. The participant then selected and opened an envelope and shared the randomization information with the dietitian, who until then

had been blinded to the group assignment. The participants (men, n = 18; women, n = 42) were randomized equally into either the intervention group or the DASH group. Recruitment and clinic staff were blinded to group assignments until after the 6-month post-intervention telephone interview. The current study was promoted as a healthy diet and lifestyle study, and study diets were identified as Diet 1 (for IER+MED) or Diet A (for DASH) to reduce any influence of familiarity with IER, MED or DASH diets.

4.3.3 Diet and Physical Activity Prescriptions

The intervention group was prescribed an IER+MED diet for 12 weeks. The IER component entailed a 70% energy restriction for two consecutive days with 34%, 33% and 33% of energy from protein, carbohydrate, and fat intakes, respectively. For the remaining five days per week, a euenergetic MED diet that met estimated energy requirements (EER), was prescribed with 25%, 45%, and 30% of energy from protein, carbohydrate, and fat, respectively. This regimen would achieve an overall energy restriction of 20% per week [22]. Participants self-selected which two consecutive days of the week to follow the IER protocol, and were asked to keep to those same two days throughout the study.

The active comparator group was prescribed a euenergetic DASH diet, which met EER, for 12 weeks, with 20%, 53%, and 30% of energy from protein, carbohydrate, and fat, respectively. An active comparator was used, instead of an inactive control, because all participants were at risk of poor metabolic conditions and would likely benefit from dietary support [34,35]. DASH was chosen as the comparator diet, as its regimen is broadly recognized as a healthful diet [36,37]. The DASH diet is rich in fruit, vegetables, low-fat dairy products, whole grains, and limits total fat, saturated fat and sodium [36,37]. All participants were advised to limit their alcohol intake, and the IER+MED group were restricted to zero alcoholic beverages on IER days. Increases in moderate to vigorous physical activity have been documented using accelerometers in past dietary interventions among intervention and control groups [38]. Therefore, to reduce confounding due to physical activity, we recommended both groups walk up to one hour per day, up to five days a week. The IER+MED group was encouraged to exercise on MED days only. EER for participants were determined based on their baseline body weight using the equations as published in the Dietary Reference Intakes (DRI) for energy for men and women 19 years and older [39]. The physical activity coefficient for men and women was assigned using the typical daily living activity descriptions from the DRI Calculator for Healthcare Professionals [40]. Information on hours in light, moderate and strenuous activity was estimated using the baseline physical activity questionnaire, which allowed dietitians to select an appropriate physical activity coefficient for each participant.

Both groups received an equal amount of planned dietitian guidance at baseline and during the intervention, although participants were encouraged to contact dietitians with any questions. The baseline face-to-face dietary consultation (45–60 minutes) with one of the three trial dietitians at the UHCC included instructions on how to follow their respective diet and physical activity plan. All participants received personalized diet booklets, individualized food lists and menus, and trackers to help them follow their plans at home. The IER+MED materials were originally developed and tested by Harvie et al. amongst white women in the UK [22,41]. Therefore, the food lists and menus were modified to provide examples of foods and beverages more commonly available in Hawaii, e.g., papaya, mango, brown rice, pak choi, sweet potato, tofu, edamame. All education materials were

designed in 100 kcal increments, e.g., 1500 kcal, 1600 kcal, 1700 kcal. For example, participants with an EER of 2030 kcal were assigned an energy allotment rounded to the closest 100 kcal, i.e., 2000 kcal. If randomized to the IER+MED group, the energy allotment would have been 2000 kcal on MED days and 600 kcal on IER days. As an example, a food group prescription on MED days for the 2000 kcal plan was 8 carbohydrate servings, 8–14 protein servings, 7 fat servings, 3 dairy servings, 6 vegetable servings, and 4 fruit servings, and a maximum of three nutrient-poor treats of ≤ 150 kcal per week. On IER days, the primary restrictions were energy and carbohydrate, and a 600 kcal plan was comprised of 2–12 protein servings, 2 fat servings, 3 dairy servings, 5 vegetables servings and 1 fruit serving. If randomized to the DASH group, using the same example as above, the diet prescription for a 2000 kcal plan was 6–8 grain servings, 4–5 fruit servings, 2–3 dairy servings, 6 meat, poultry, or fish servings, 4–5 nuts, seeds, or legumes servings, 2–3 fats or oils servings, a maximum sodium intake of 2300 mg per day, and 5 or less sweets and added sugars servings per week. The personalized diet booklets detailed the amounts for servings of each food group and provided examples of types of foods to choose from within each food group. To support the dietary counseling, study dietitians underwent training in behavioral change strategies using the Body and Soul program [42–44]. In particular, the training focused on motivational interviewing techniques, ensuring the dietitians practiced reflective listening and provided positive affirmations rather than relying heavily on persuasion or advice giving [42–44]. Dietitians contacted participants at Weeks 1, 2, 3, 4, 6, 8 and 10, primarily by telephone, and met in person with participants during the final clinic visit, to assess participants' compliance to the intervention plans and guide positive behavioral change.

4.4.4 Study Measurements

Dietary intakes were assessed using the mFR™ completed at baseline, between Weeks 5–6, and at Week 11. The mFR™ is designed to capture images of foods/beverages before and after each eating occasion and allows for automatic uploading of images to a secure cloud-based server when in 3G/4G/Wi-Fi range [28–31]. During the eligibility visit, the mFR™ app was loaded onto each participant's mobile device by a study dietitian. Participants were trained on how to use the mFR™ and provided with a fiducial marker (a small reference device of known dimensions and colors) to include in images [30,31]. All participants were asked to use the mFR™ over four contiguous days including at least one weekend day to capture a baseline mFR™ between the eligibility and baseline clinic visits. After the baseline clinic visit, participants in the IER+MED group were asked to keep mFRs™ of their two IER days bookended by two MED days, e.g., MED-IER-IER-MED at Weeks 5–6 and Week 11. Participants in the DASH group were asked to keep to the same recording days as their baseline record for recording their Weeks 5–6 and Week 11 mFRs™. Images from the mFR™ were reviewed in person with a dietitian at the baseline and the final clinic visits, and over the phone at Week 6. All participants were willing to download the app, except five could not due to owning an incompatible phone (n = 3), full phone memory (n = 1), or phone lacking features to run app (n = 1). Consequently, these five participants completed written records [45,46]. Data entry of before and after images of food and beverages followed the methods by Kerr et al [29,47]. Briefly, dietitians underwent analyst training before entering the food and beverage data into RapidCalc, a dietary data entry program developed at UHCC [48,49]. Training consisted of identifying the amount and type of food in test mFR™

images. This task was completed with the assistance of a fiducial marker [50] for size estimation, and an additional foods questionnaire (completed by participants at baseline) to help identify occluded foods, e.g., type of milk in tea or coffee. A priori, only dietary records with at least two days of recording and at least one eating occasion captured on each day were to be included in the analysis.

Clinic measures were taken at baseline and Week 12. Anthropometric, body composition, fasting bloods, and blood pressure measures were collected using the same protocol as Lim et al [11]. Briefly, whole-body composition was determined by DXA (Hologic Discovery A fan-beam densitometer, Hologic Inc. (Bedford, MA, USA) using APEX 3.3). Fat mass and lean mass were estimated for the whole body, trunk, arms, and legs, from which skeletal muscle mass was derived [51,52,53]. For VAT and SAT outcomes, we used visceral and subcutaneous fat area estimates for L4-L5 derived from DXA parameters. Trained technicians obtained measurements of height, weight, and circumferences of the waist and hip. Fasting blood samples were processed at the UHCC and analyzed at the UHCC Analytical Biochemistry Shared Resource Laboratory for plasma levels of total cholesterol, high-density (HDL and low-density (LDL) cholesterol, glucose, insulin, alanine transaminase (ALT), and aspartame transaminase (AST). Blood pressure in the left arm was measured in a sitting position after 20 minutes of rest using a digital monitor (Omron HEM-907XL, Omron Healthcare, Inc. (Lake Forest, IL, USA)). Physical activity levels (PALs) were assessed at baseline using a physical activity questionnaire previously validated for the MEC [54]. The questionnaire was designed to reflect average physical activity per day completed in the preceding year, including moderate-to-vigorous activity [54]. The baseline physical activity questionnaire was modified for the Week 12 visit, with participants being asked to recall physical activity in the preceding week.

During the telephone calls at Weeks 1, 2, 3, 4, 6, 8 and 10, and the in person visit at Week 12, participants in the IER+MED group self-reported how many IER days they had successfully completed in the most recent week, i.e., 0, 1, or 2 days. All participants were also asked, "How well have you been following your diet plan? On a scale of zero to ten with zero being not at all, four being somewhat, and ten being following the plan very well, where would you place yourself?" and "How well have you been following your physical activity plan? On a scale of zero to ten with zero being not at all, four being somewhat, and ten being following the plan very well, where would you place yourself?". Participants were also encouraged to report any minor or major adverse effects experienced during the study (e.g., adverse reactions associated with performing DXA, phlebotomy, or from following the diet).

4.4.5 Six-Month Post-Intervention Telephone Interview

At 6 months post-intervention, participants who completed the study were interviewed over the telephone. These calls were conducted by trained recruitment staff not involved in the 12-week intervention counseling. Quantitative questions included current weight, still following the intervention diet plan (yes/no) and extent (same, better, not as well), willingness to follow the prescribed diet longer than 3 months (yes/no), and interest in nutrition/food preparation classes (yes/no). Open-ended qualitative questions related to current health issues, physical activity, description of type of diet currently being followed, and suggestions on how the study could be improved were also asked. This paper summarizes and reports only the responses to the quantitative questions.

4.4.6 Statistical Analysis

Continuous variables are reported as means ± SDs or SEMs, and categorical variables are reported as counts and percentages. The analysis followed an intention-to-treat-analyses, where all individuals were analyzed in a randomization group, regardless of compliance. A linear mixed model was fit for each outcome. This model uses of all available data to estimate the treatment effects over time using maximum likelihood estimation under a missing-at-random assumption [55,56]. The model included an indicator variable for intervention group (IER+MED vs. DASH), indicator variable for time (Week 12 vs. baseline, or Weeks 5–6 vs. baseline and Week 11 vs. baseline for diet), and interaction terms between group and time. The F test was used to assess the intervention effect, defined as the contrast of change in IER+MED minus change in DASH. Outcome variables included: dietary intakes, body measurements, biomarkers, and physical activity. The following comparisons were made across time points: Week 12 vs. baseline for body measurements, physical activity, and biomarkers, and Weeks 5–6 vs. baseline, Week 11 vs. baseline, and Weeks 5–6 vs. Week 11 for diet. No transformations of the outcomes were needed to meet model requirements as values for change over time were approximately normal and homoscedastic. To test the specific effects of the IER+MED intervention on VAT and biomarkers independent of those on total adiposity, additional models were run adjusting for concurrent total fat mass. Model-predicted adjusted means at each time point for each group were computed. Diet data are represented as group mean daily intakes. For DASH, the mean across four food record days were taken, while for the IER+MED group, means were computed by IER and MED days and then an overall average was computed, weighting the IER mean by 2 and the MED mean by 5. Per protocol analyses, changes in diet and body measurements were also conducted only among those completing the intervention (i.e., had a Week 12 assessment). For per protocol analyses, diet data were also reported separately for IER and MED days. To verify the reported change in energy intake over time, for both study groups, the expected weight change at 12 weeks was compared to measured weight change at Week 12. An energy deficit of 500 to 1000 kcal/day is estimated to result in a weight loss of 0.45 to 0.90 kg/week [57,58]. The average difference per day between energy intakes at baseline and Week 11 was estimated as the average of the change from baseline to Weeks 5–6 and the change from Weeks 5–6 to Week 11, which were calculated from a mixed model of energy on time, for both groups. The average change in weight in pounds was then calculated as the estimated change in energy per day from baseline to Week 11 converted to pounds of weight loss as [change in energy/500] x 12 weeks. A 95% confidence interval for change in weight was computed by converting the limits of a 95% confidence interval for change in energy.

Alcohol, vitamin and mineral intake, and the proportion of participants meeting the US estimated average requirement (EAR) for vitamin and mineral intake at baseline, Weeks 5–6 and 11 are reported for both groups. Statistical significance was defined as $p < 0.05$. Data were analyzed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA) and IBM SPSS Statistics version 25 software (IBM Corp., Armonk, NY, USA).

4.5 Results

4.5.1 Study Population

The stratified randomized sampling was successful, with men and women being distributed evenly between groups, and participants with high (< 150 cm^2) and very high (≥ 150 cm^2) VAT being distributed almost equally between groups (Table 4.1). After 12 weeks, four participants dropped out of the IER+MED group and two out of the DASH group; therefore, 87% (n = 26) of participants in the IER+MED group and 93% (n = 28) in the DASH group completed the study (Figure 4.1). One participant from the IER+MED group dropped out due to not being able to adhere to the diet and the other five participants dropped out for reasons unrelated to the study (e.g., work, medical reasons). There were no major adverse effects reported during the intervention.

Table 4.1 Randomization and baseline characteristics of study participants by the intermittent energy restriction combined with a Mediterranean diet (IER+MED) and dietary approaches to stop hypertension (DASH) groups.

Variable	**Randomization Group**	
	IER+MED (n = 30)	**DASH (n = 30)**
Men	9	9
Visceral adipose tissue category (%)		
High (90 < 150 cm^2)	6 (67%)	6 (67%)
Very high (≥ 150 cm^2)	3 (33%)	3 (33%)
Women	21	21
Visceral adipose tissue category (%)		
High (80 < 150 cm^2)	13 (62%)	14 (67%)
Very high (≥ 150 cm^2)	8 (38)	7 (33%)
Characteristics (Men and Women)		
Age (years)	48.4 ± 4.7	46.2 ± 5.4
Height (m)	1.6 ± 0.1	1.6 ± 0.1
Weight (kg)	79.3 ± 12.5	81.0 ± 12.5
Visceral adipose tissue area (cm^2)	134.6 ± 6.4	135.3 ± 6.4
Body mass index (kg/m^2)	30.5 ± 3.5	30.8 ± 3.3
Moderate or vigorous physical activity (hours/day)	1.6 ± 0.2	1.4 ± 0.3
Ethnicity (%)		
Chinese	23.3	6.7
Japanese	56.7	63.3
Korean	10.0	13.3
Mixed Asian	10.0	16.7

Data are presented as mean ± standard deviation (SD) or number (%). IER+MED: Intermittent energy restriction combined with a Mediterranean diet. DASH: Dietary Approaches to Stop Hypertension diet.

4.5.2 Intervention Adherence

The IER+MED participants completed 90.6% of the allocated IER days. Ninety six percent of these IER days were completed as two consecutive IER days and the remainder completed at least one IER day per week. For the IER+MED group, the mean self-rated compliance to the diet prescription and the self-rated compliance to the physical activity prescription were 7.7 at Week 1, Week 6, and Week 12 using the scale of 0–10. For the DASH group, the respective self-rated compliance rates were 6.7, 6.8, and 6.4 for diet and 6.4, 7.3, and 6.9 for physical activity. Data from the physical activity questionnaires support there being no significant change in physical activity from baseline to Week 12 for within the IER+MED group (1.58 ± 0.22 to 1.43 ± 0.23 hours of moderate or vigorous activity/day,

respectively, $p = 0.49$) and the DASH group (1.39 ± 0.22 to 1.27 ± 0.22 hours of moderate or vigorous activity/day, $p = 0.58$) or between groups ($p = 0.91$). Both groups met the physical activity recommendations at the beginning and end of the intervention.

Overall, there was a 23% decrease in mean daily energy intake for the IER+MED group from baseline (1,590 kcal) to Weeks 5–6 (1227 kcal), and a 28% decrease between baseline and Week 11 (1152 kcal) (Table 4.2). Mean energy allotment for the IER days was 692 kcal (range 540 to 960 kcal). Estimated mean energy intakes on IER days were 960 kcal at Weeks 5–6 and 929 kcal at Week 11 (Appendix B). For the MED days, the mean energy allotment was 2307 kcal (range 1800 to 3200 kcal). Estimated mean energy intakes on MED days were 1222 kcal at Week 5–6 and 1144 kcal at Week 11. For the DASH group, energy intake decreased by 22% between baseline (1803 kcal) and Weeks 5–6 (1414 kcal) and by 16% between baseline and Week 11 (1507 kcal) as seen in Table 4.2. Mean energy allotment was 2300 kcal (range 1800 to 3400 kcal).

The prescriptions for percentage energy from protein, carbohydrates and total fats for the IER+MED group were approximately 28%, 42%, and 31%, respectively (weighted for two IER days and five MED days). By Week 11, participants in this group increased their percentage energy from protein from 18.7% to 25.7%, almost matching the prescription of 28%. The mean percentage energy from carbohydrates decreased from 44.8% to 35.1% which was lower than the goal of 42%. Percentage energy from total fats increased from 36.6% to 40.2%, as compared to the recommended of 31%. When examined as absolute intake, participants in the IER+MED decreased their mean intakes of total fats from 64.7 g at baseline to 51.8 g at Week 11, and their mean intakes of carbohydrates from 180 g to 103 g. Since the drop in grams of carbohydrates was proportionally larger than the drop in total fats, percentage of energy from carbohydrates decreased and percentage energy from total fats increased. For the DASH group the recommended percentage energy from protein, carbohydrates and total fats was 20%, 53%, and 30%, respectively. By Week 11, the DASH group increased percentage energy from protein from 17.3% to 18.9%, with the goal of reaching 20%. At baseline, percentage energy from carbohydrates and total fats were 44.1% and 38.3%, respectively, and did not significantly change by Week 11. Assessing absolute intakes, mean carbohydrate intakes dropped from 198 g to 169 g and mean intakes of total fats decreased from 77.6 g to 62.7 g. Total energy intake also decreased by Week 11; therefore, the drop in grams of carbohydrates and total fats consumed did not affect percentage of energy from these macronutrients. For both the IER+MED and DASH groups there were no significant changes in total energy (kcal); percentage energy from total protein, fat, or carbohydrate; and grams of protein, fat, or carbohydrate consumed between Weeks 5–6 and Week 11. In per protocol analyses, similar patterns were seen (Appendix B).

At Week 11, and only among the IER+MED group, reductions in calcium, thiamin, and folate intakes were observed, as well as, the proportion of participants meeting the EAR for calcium, thiamin, and folate (Appendix I-J). A more detailed description of alcohol and micronutrient intake and proportion of participants meeting the EAR for micronutrients can be found in the Appendices (Appendix I-J).

Table 4.2 Dietary intake assessed using 4-day mobile food records (mFR™) captured by participants in the IER+MED group (n = 30) and the DASH group (n = 30) across three time points [1].

Variable	Baseline	Weeks 5–6	p [2]	Week 11	p [3]
Energy (kcal)					
IER+MED [4]	1590 ± 078	1227 ± 085	<0.0001	1155 ± 077	<0.0001
DASH	1803 ± 111	1414 ± 096	0.001	1507 ± 100	0.001
Protein (g)					
IER+MED	73.0 ± 3.6	74.9 ± 5.0	0.692	72.7 ± 4.2	0.946
DASH	76.5 ± 4.6	66.1 ± 4.8	0.055	70.6 ± 4.7	0.128
Protein (% energy)					
IER+MED	18.7 ± 0.7	24.9 ± 1.0	<0.0001	25.7 ± 1.1	<0.0001
DASH	17.3 ± 0.6	18.7 ± 0.5	0.115	18.9 ± 0.5	0.011
Carbohydrate (g)					
IER+MED	180 ± 11	115 ± 10	<0.0001	103 ± 09	<0.0001
DASH	198 ± 13	160 ± 12	0.013	169 ± 12	0.008
Carbohydrate (% energy)					
IER+MED	44.8 ± 1.5	37.3 ± 1.6	<0.0001	35.1 ± 1.6	<0.0001
DASH	44.1 ± 1.2	44.8 ± 1.1	0.650	45.2 ± 1.3	0.418
Total fat (g)					
IER+MED	65 ± 4	53 ± 5	0.015	52 ± 4	0.001
DASH	78 ± 6	57 ± 4	<0.0001	63 ± 5	0.001
Total fat (% energy)					
IER+MED	36.6 ± 1.1	39.1 ± 1.4	0.140	40.2 ± 1.2	0.014
DASH	38.3 ± 1.1	36.7 ± 1.1	0.183	36.8 ± 1.3	0.234
Saturated fatty acids (% energy)					
IER+MED	11.5 ± 0.4	11.1 ± 0.6	0.560	11.6 ± 0.6	0.854
DASH	11.7 ± 0.5	11.0 ± 0.4	0.092	11.8 ± 0.5	0.830
Monounsaturated fatty acids (% energy)					
IER+MED	13.6 ± 0.4	15.0 ± 0.6	0.055	15.9 ± 0.6	0.001
DASH	14.5 ± 0.5	13.6 ± 0.5	0.111	13.9 ± 0.6	0.357
Polyunsaturated fatty acids (% energy)					
IER+MED	8.4 ± 0.5	9.6 ± 0.5	0.093	8.8 ± 0.5	0.426
DASH	9.0 ± 0.5	9.0 ± 0.6	0.994	7.7 ± 0.4	0.093
Dietary fiber (g)					
IER+MED	13.0 ± 1.0	12.8 ± 0.9	0.874	11.9 ± 1.0	0.297
DASH	13.4 ± 1.1	14.1 ± 1.3	0.661	13.7 ± 1.0	0.814

Data are presented as mean/day ± standard error of the mean (SEM). IER+MED: Intermittent energy restriction combined with a Mediterranean diet. DASH: Dietary Approaches to Stop Hypertension diet.[1] All data analyzed using an intention-to-treat approach with a linear mixed model for all 60 participants. [2] Within group difference from baseline to Weeks 5–6. [3] Within group difference from baseline to Week 11. [4] Weighted for five Mediterranean diet (MED) days and two intermittent energy restriction (IER) days.

4.5.3 Changes in Anthropometric, DXA, and Biomarker Measurements at Week 12

Both the IER+MED and the DASH groups experienced significant reductions in all anthropometric and DXA measurements from baseline to Week 12 (Table 4.3). Between groups, the IER+MED group had a significantly greater loss of weight, BMI, waist circumference, hip circumference, percentage body fat, fat mass, muscle mass, total lean body mass, VAT, and SAT compared to the DASH group (Table 4.3). These decreases in anthropometric and DXA measures were close to double for the IER+MED group compared to the DASH group and over three times the amount for change in SAT. In the IER+MED group, approximately 73% of participants lost 5% or greater of their weight and 27% of participants lost 10% or greater of their weight. In the DASH group, these were 32% and 7%, respectively. Per protocol analyses, showed similar results for change in anthropometric and DXA measurements between and within groups (Appendix K). After adjusting for concurrent total fat mass, change in VAT was no longer significantly different between groups (IER+MED −8.6 ± 3.1 cm^2 vs. DASH −3.7 ± 2.6 cm^2, $p = 0.188$). The VAT/SAT ratio did not change significantly for either group between baseline and Week 12 (Table 4.3). Based on the average difference per day between energy intakes at baseline and Week 11, and the guidelines of an energy deficit of 500 to 1,000 kcal/day is estimated to result in a weight loss of 0.45 to 0.90 /week, the expected mean (95% CI) weight loss for the IER+MED group at Week 12 was 5.1 (2.5–7.8) kg. Actual mean weight loss at Week 12 was 5.9 kg; therefore, fell within the expected range. For the DASH group, expected mean weight loss at Week 12 was 3.6 (0.2–6.9) kg. Actual weight loss was 3.3 kg; therefore, also fell within the expected range. All fasting blood biomarkers (total and LDL cholesterol, triglycerides, insulin, ALT, and AST), except HDL cholesterol, and systolic and diastolic blood pressure significantly improved in the IER+MED group, whereas only triglycerides, insulin, and blood pressure improved in DASH (Table 4.4). Only the improvement in ALT was significantly greater in the IER+MED group compared to the DASH group ($p = 0.04$), which was maintained after adjusting for concurrent total fat mass (−16.2 ± 3.8 U/L vs. −4.0 ± 3.6 U/L, respectively) ($p = 0.02$).

Table 4.3 Baseline, Week 12, and change in anthropometric measures within and between the IER+MED group (n = 30) and DASH group (n = 30) [1].

Variable	Baseline	Week 12	p [2]	Change	p [3]
Weight (kg)					
IER+MED	79.3 ± 2.2	73.4 ± 2.2	<0.0001	−5.9 ± 0.7	0.007
DASH	81.0 ± 2.2	77.8 ± 2.2	<0.0001	−3.3 ± 0.6	
Body mass index (kg/m^2)					
IER+MED	30.5 ± 0.6	28.3 ± 0.6	<0.0001	−2.2 ± 0.2	0.002
DASH	30.8 ± 0.6	29.6 ± 0.6	<0.0001	−1.2 ± 0.2	
Waist circumference (cm)					
IER+MED	100.3 ± 1.6	93.3 ± 1.6	<0.0001	−6.9 ± 0.8	0.026
DASH	100.7 ± 1.6	96.2 ± 1.6	<0.0001	−4.5 ± 0.7	
Hip circumference (cm)					
IER+MED	107.7 ± 1.3	102.5 ± 1.3	<0.0001	−5.3 ± 0.5	0.021
DASH	107.3 ± 1.3	103.9 ± 1.3	<0.0001	−3.4 ± 0.5	
Body fat (%)					
IER+MED	33.4 ± 1.2	31.3 ± 1.2	<0.0001	−2.0 ± 0.4	0.021
DASH	33.0 ± 1.2	32.1 ± 1.2	0.023	−0.8 ± 0.4	
Fat mass (kg)					
IER+MED	26.4 ± 1.1	23.1 ± 1.1	<0.0001	−3.3 ± 0.4	0.005
DASH	26.4 ± 1.1	24.9 ± 1.1	<0.0001	−1.6 ± 0.4	
Muscle mass (kg)					
IER+MED	21.9 ± 0.9	20.8 ± 0.9	<0.0001	−1.1 ± 0.2	0.013
DASH	22.3 ± 0.9	21.8 ± 0.9	0.005	−0.5 ± 0.2	
Total lean body mass (kg)					
IER+MED	52.6 ± 1.8	50.4 ± 1.8	<0.0001	−2.3 ± 0.4	0.040
DASH	54.3 ± 1.8	53.1 ± 1.8	0.002	−1.2 ± 0.4	
Visceral adipose tissue area (cm^2)					
IER+MED	134.6 ± 6.4	112.0 ± 6.5	<0.0001	−22.6 ± 3.6	0.022
DASH	135.3 ± 6.4	124.5 ± 6.5	0.003	−10.7 ± 3.5	
Subcutaneous adipose tissue area (cm^2)					
IER+MED	373.1 ± 16.2	324.9 ± 16.4	<0.0001	−48.2 ± 6.4	<0.0001
DASH	359.0 ± 16.2	344.0 ± 16.3	0.018	−15.0 ± 6.1	
VAT/SAT ratio [4]					
IER+MED	0.38 ± 0.02	0.36 ± 0.02	0.157	−0.01 ± 0.01	0.825
DASH	0.39 ± 0.02	0.37 ± 0.02	0.076	−0.01 ± 0.01	

Data are presented as mean ± standard error of the mean (SEM). IER+MED: Intermittent energy restriction combined with a Mediterranean diet. DASH: Dietary Approaches to Stop Hypertension diet. [1] All data analyzed using an intention-to-treat approach with a linear mixed model for all 60 participants. [2] Within group difference from baseline to Week 12. [3] Between group difference (IER+MED vs. DASH) from baseline to Week 12. [4] Ratio of visceral adipose tissue area to subcutaneous adipose tissue area.

Table 4.4 Baseline, Week 12, and change in metabolic risk biomarkers within and between the IER+MED group (n = 30) and the DASH group (n = 30) [1].

Variable	Baseline	Week 12	p [2]	Change	p [3]
Cholesterol (mg/dL)					
IER+MED	237.0 ± 10.3	219.5 ± 10.3	0.009	−17.4 ± 6.4	0.356
DASH	250.0 ± 10.0	240.9 ± 10.0	0.149	−9.1 ± 6.2	
HDL cholesterol (mg/dL)					
IER+MED	38.1 ± 2.4	39.6 ± 2.4	0.396	1.5 ± 1.8	0.610
DASH	32.1 ± 2.3	34.9 ± 2.3	0.110	2.8 ± 1.7	
LDL cholesterol (mg/dL)					
IER+MED	178.5 ± 9.2	164.5 ± 9.2	0.019	−14.0 ± 5.8	0.585
DASH	188.6 ± 9.1	179.1 ± 9.1	0.104	−9.5 ± 5.8	
Triglycerides (mg/dL)					
IER+MED	101.9 ± 26.2	77.1 ± 26.2	0.004	−24.8 ± 8.2	0.809
DASH	165.5 ± 25.2	143.5 ± 25.2	0.008	−22.0 ± 7.9	
Alanine transaminase (U/L)					
IER+MED	33.8 ± 3.2	20.1 ± 3.2	0.001	−13.8 ± 3.7	0.038
DASH	19.5 ± 3.1	16.6 ± 3.1	0.419	−2.9 ± 3.6	
Glucose (mg/dL)					
IER+MED	104.3 ± 4.2	102.2 ± 4.2	0.374	−2.1 ± 2.4	0.928
DASH	104.9 ± 4.1	102.5 ± 4.1	0.294	−2.4 ± 2.3	
Aspartame transaminase (U/L)					
IER+MED	23.8 ± 1.8	18.1 ± 1.8	0.012	−5.7 ± 2.2	0.179
DASH	18.9 ± 1.7	17.3 ± 1.7	0.462	−1.6 ± 2.1	
Insulin (mU/L)					
IER+MED	13.9 ± 1.7	8.8 ± 1.7	<0.001	−5.1 ± 1.2	0.134
DASH	14.6 ± 1.6	12.0 ± 1.6	0.027	−2.5 ± 1.7	
Systolic blood pressure (mm Hg)					
IER+MED	133.2 ± 2.5	124.3 ± 2.7	<0.001	−9.0 ± 2.5	0.345
DASH	133.4 ± 2.5	127.7 ± 2.6	0.024	−5.7 ± 2.4	
Diastolic blood pressure (mm Hg)					
IER+MED	84.2 ± 1.7	77.5 ± 1.8	<0.001	−6.7 ± 1.5	0.124
DASH	86.2 ± 1.7	82.8 ± 1.8	0.021	−3.4 ± 1.4	

Data are presented as mean ± standard error of the mean (SEM). IER+MED: Intermittent energy restriction combined with a Mediterranean diet. DASH: Dietary Approaches to Stop Hypertension diet. [1] All data analyzed using an intention-to-treat approach with a linear mixed model for all 60 participants. [2] Within group difference from baseline to Week 12. [3] Between group difference from baseline to Week 12.

4.5.4 Six-month Post-Intervention Telephone Interview

Among participants completing the 6-month post-intervention telephone interview, for the IER+MED group there was no significant change in body weights measured at Week 12 and self-reported at 6 months post study (Table 4.5). For the DASH group there was a significant increase in body weights (p = 0.03). During the post-intervention telephone call, both the IER+MED and DASH groups reported physical activity of over 3.5 hours/week (mean). In addition, 71.4% of participants in the IER+MED group, compared to 88.0% in the DASH group, reported they were able to follow the prescribed diet longer than three months after the study finished (Table 4.5). The mean amount of time participants could follow the diet prescription was 5.0 months for the IER+MED group vs. 3.6 months for the DASH

group. In addition, almost two-thirds, 66.7%, of participants in the IER+MED group were still following their diet prescription at the time of the post-intervention telephone call, with 6.7% reporting they were still following the diet protocol the same as they were when completing the study. For the DASH group, 44.0% of participants were still following their diet prescription at the time of the post-intervention telephone call and 25.0% reported they were still following the diet protocol the same as during the study.

Table 4.5 Self-reported data collected during the 6-month post-intervention telephone interview for participants in the IER+MED group (n = 22) and the DASH group (n = 26), who completed the intervention.

Variable	***IER+MED***	***DASH***
Weight (kg)	*75.5 ± 2.7*	*77.9 ± 3.2*
Change in weight between Week 12 [1] and 6-month post-intervention (kg) [2]	*1.0 ± 3.8*	*1.1 ± 2.1**
Physical activity (hours/week)	*3.8 ± 0.4*	*3.6 ± 0.6*
Able to follow the diet prescription for longer than 3 months (%)		
No	*28.6*	*12.0*
Yes	*71.4*	*88.0*
If yes, for how many more months?	*5.0 ± 0.6*	*3.6 ± 0.5*
Still following the diet prescription (%)		
No	*33.3*	*56.0*
Yes	*66.7*	*44.0*
If yes, following the diet the same, better, not as well, or other (%)		
Same	*6.7*	*25.0*
Better	*0.0*	*0.0*
Not as well	*80.0*	*66.7*
Same and not as well	*13.3*	*0.0*
Other	*0.0*	*8.3*
Would nutrition classes and/or food preparation classes been helpful (%)		
No	*13.6*	*24.0*
Yes	*86.4*	*76.0*

Data are presented as mean ± standard deviation (SD) or number (%). IER+MED: Intermittent energy restriction combined with a Mediterranean diet. DASH: Dietary Approaches to Stop Hypertension diet. [1] Weight measured at Week 12 visit. [2] Analyses completed using paired samples t-tests. * $p \leq 0.03$.

4.6 Discussion

This is the first known pilot study to evaluate the effectiveness of a culturally adapted IER+MED vs. an active comparator (DASH diet) to reduce DXA measured VAT among East Asian Americans. This study was also unique in that the mFR was used to capture dietary intake. Despite the IER+MED diet being different to traditional and acculturated Asian diets, participants complied well to prescriptions. For both study arms, the recommendations, which appeared most difficult to achieve were those for carbohydrate and fat, with percentage of energy from carbohydrates being consistently lower than recommended and percentage of energy from total fats being consistently higher. Despite reductions in energy intake, the proportion of fiber in the diet, for the IER+MED and DASH groups, was higher at Week 12 than baseline. Both study groups had significant reductions in VAT, weight, and total adiposity. Although loss of VAT was greater in IER+MED than in DASH, this appeared to be due to the greater loss of total fat in IER+MED as there was no significant group

difference after adjusting for concurrent total fat mass. For IER+MED, we observed general improvements in metabolic risk biomarkers, particularly in total and LDL cholesterol, triglycerides, ALT, AST, insulin, systolic and diastolic blood pressure. Only the reduction in ALT was significantly greater in IER+MED vs. DASH, a difference maintained after adjusting for concurrent total fat mass. This indicates a potentially greater benefit of IER+MED on liver function, compared to a healthful dietary pattern [59]. The observed results were not due to differences in physical activity as both groups reported similar levels of physical activity at the beginning and end of the intervention, and these levels met the physical activity recommendations. This pilot study demonstrated that an IER+MED vs. DASH intervention can be successfully conducted with East Asian Americans, and with a low attrition rate of 10%.

Consistent with our results, other IER trials involving two energy restricted days as consecutive or non-consecutive restricted days (termed "5:2"[55]) have reported high study retention and protocol adherence [22,55,60,61]. Attrition rates range from 4.2% to 23% [22,55,60,61], which supports observations of participants being able and willing to complete "5:2" trials. In the "5:2" study by Harvie et al, a study arm was prescribed a 70% energy restriction for two consecutive days and 5 non-restricted days following a euenergetic MED diet [22]. Over three months, participants in the IER study arms in the Harvie et al trial completed 74–76% of their two IER days, indicating high study compliance [22]. Similarities between the current study and the Harvie et al. trials were energy intake was higher than prescribed on IER days, and energy and carbohydrate intakes were lower than prescribed on non-restricted days [22]. This highlights that participants do well at completing their IER days, but may need extra support with meeting their energy and carbohydrate prescriptions. Results from the current study also support previous findings that participants do not over eat on non-restricted days [18,22]. Harvie et al [22] hypothesized that the reduced intake on non-restricted days could be due to behavioral aspects of following IER (e.g., IER made participants more aware of habitual intakes, and increased awareness of appetite and hunger). Also, for both groups, dietitians promoted consuming high quality unprocessed diets on euenergetic days, which may have resulted in participants consuming less energy than prescribed [62]. As part of the post-intervention follow up call, the majority of participants from both groups reported nutrition classes and/or food preparation classes would have been helpful. Incorporating nutrition classes and/or food preparation classes may be a useful strategy to improve compliance to dietary prescriptions [63].

We observed no preferential loss of VAT in the IER+MED group compared to the DASH group after adjusting for concurrent total fat mass. The results of this analysis could be clinically true if the DASH group was able to lose similar amounts of fat mass to the IER+MED group and maintain this loss. However, results suggest that IER+MED is easier to follow than the euenergetic DASH, and weight loss easier to maintain. For example, self-rated dietary compliance scores were higher for IER+MED (7.7 at Weeks 1, 6 and 12) compared to DASH (6.7, 6.8, and 6.4, respectively), and at 6-months post-intervention 66.7%, of the IER+MED group vs. 44.0% of the DASH group reported still following their diet prescriptions. In addition, between the Week 12 visit and the 6-month post-intervention telephone interview, amongst participants completing the call, self-reported weight suggested that weight loss was maintained in the IER+MED group and that weight increased in the DASH group. These results are promising as CER is known to be difficult to follow long term [16]; therefore, IER may be an easier alternative to adopt.

VAT data were not collected at 6-months post intervention; however, given the self-report of weight maintenance, it is likely that loss of VAT was also maintained in the IER+MED group [15]. The only known "5:2" IER trial to assess the effect of IER on VAT is the HELENA trial carried out over 50 weeks [55]. This trial found that IER did not exert stronger effects on VAT loss than CER [55]; however, their trial incorporated two non-consecutive restriction days. Incorporating two consecutive vs. non-consecutive restriction days may have differing effects on health outcomes. The former may likely produce higher reductions on insulin resistance and percentage body fat [22,55]. Therefore, further long term studies are needed to assess the effects of "5:2" trials with 2 consecutive restriction days on VAT. The IER+MED and DASH groups reduced VAT proportionally to their change in total adiposity and the difference between groups may be due to the difference in energy intakes. Diets limited in sodium and more in line with the DASH diet, have been associated with lower VAT [27,64], which likely contributed, along with the observed decrease in energy intake, to the loss of VAT in the DASH group. These improvements in VAT may explain the lack of significant difference between groups in most metabolic risk biomarkers. The greater improvement in ALT in the IER+MED group vs. the DASH group is important as ALT is a biomarker for NAFLD [59]. Significant reductions in ALT in the IER+MED group even after adjusting for change in total adiposity suggest improvements in liver function, beyond that obtained by VAT reduction alone [59]. However, liver fat measurement e.g., by abdominal MRI scans are needed to confirm this. The decrease in ALT when following IER+MED is consistent with the European guidelines for NAFLD, which recommend following a MED diet and energy restriction to improve NAFLD [26].

For the IER+MED group, there was a reduction in dietary calcium, thiamin, and folate intakes, and in the proportion of participants meeting the EAR for calcium, thiamin, and folate. Past "5:2" studies have also reported reductions in micronutrients [22,61]; for example, Harvie et al expressed concern about lower intakes of calcium, iron, zinc, vitamins A and D and fiber in the IER groups [22]. Previous "5:2" trials, have prescribed a healthful diet [22,55] or recommended participants follow their usual diet [60,61] on non-restricted days. Given the large energy deficit on restricted days, prescribing a balanced diet on non-restriction days along with a nutritional supplement may help to limit any possible deficiencies. In the current study, blood measurements to assess nutritional deficiencies were not completed. Across "5:2" trials, including the current study, there were no reported serious adverse effects [22,55,61].

The strengths of the design for the current study include the stratified random design, the inclusion of an active comparator, blinding of participants and study staff (other than dietitians) to group allocations, the ethnic/racial tailoring of the intervention prescriptions, and providing the same physical activity recommendations for both study arms. Another strength was the low attrition rate, which added to the validity and reliability of study results. The reliability is evident from the similarity in results between the intention-to-treat analyses using all participants (n = 60) and the per protocol analyses using only participants who completed the study (n = 54). Additional strengths were the use of the mFR™ for assessing dietary intake, which was used to help generate responses to study promotions, encourage adherence during the intervention, and allowed the intervention dietitians to monitor dietary intakes in real time [28–30,65], and the novel use of DXA to measure VAT.

Limitations of the current pilot study include the small sample size, which may have limited statistical power to show small differences between groups. Also, the possible misreporting of dietary intake, with underreporting of dietary intakes being common

among people with overweight or obesity [66,67]. However, weight loss achieved by participants in the IER+MED and DASH groups corresponded well to the average change in daily energy intake between baseline and Week 11, indicating at the group level, the dietary data was collected and analyzed accurately [57,58]. Another limitation is that results from the 6-month post-intervention telephone interview may not be representative of the study sample due to not all participants responding and the self-reported nature of the information collected. There have been limited studies comparing DXA-based VAT measures with CT or MRI and, in the few studies reported, the DXA results overestimated VAT, particularly in individuals with higher VAT levels [68–70].

4.7 Conclusions

In summary, this randomized pilot study, testing the effects of IER+MED vs. an active comparator DASH diet on VAT levels, was successfully conducted among a relatively small sample of East Asian Americans in Hawaii. Despite the prior belief among the investigators that the IER+MED diet would be challenging to adopt among East Asian Americans, the participants complied well to the culturally adapted study prescriptions and the attrition rate was low. Visceral adiposity, as well as total fat mass and ALT, were reduced to a greater extent in the IER+MED diet group than in the DASH diet group, possibly because the observed decrease in energy intake was greater in the IER+MED group. Within groups, changes in VAT may have resulted from changes in macronutrient intakes. IER+MED was superior to DASH in improving ALT since this improvement was not explained by the greater reduction in total fat mass. The results of this pilot study are promising, and further studies addressing a larger sample of men and women are needed to confirm the effectiveness of the IER+MED diet on change in VAT, and its possible beneficial effect on liver fat, in the short term and long term.

Author Contributions: Author contributions included; L.L.M. conceived the study; U.L., K.M.Y., K.D.C, L.R.W, M.N.H, L.L.M, G.M, J.W.L, and C.J.B. collaborated on the design of the research; C.E.P., L.R.W., and C.J.B. analyzed the data; C.E.P, U.L, K.M.Y, K.D.C, L.R.W, M.N.H, G.M, E.J.D, J.W.L, J.A.S, L.L.M, and C.J.B. assisted with data analysis and interpretation of results, and wrote the manuscript.

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CHAPTER 5. DIET QUALITY IS ASSOCIATED WITH LOWER VISCERAL AND OVERALL ADIPOSITY AMONG A MULTIETHNIC ADULT POPULATION

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5.1 Abstract

Visceral adiposity, more so than overall adiposity, is associated with chronic disease and mortality. Known determinants of visceral adiposity include age, sex, ethnicity, and diet quality. There is little research exploring the association between diet quality and visceral adiposity among a multiethnic adult population. This cross-sectional analysis examined the association between diet quality (Healthy Eating Index-2010 (HEI-2010) scores) and DXA-based visceral adipose tissue (VAT), overall adiposity, and blood-based biomarkers of metabolic risk. 540 adults (18-80 y; white, African American, Asian, Latino, Native Hawaiian or Other Pacific Islander) were recruited across 3 sites (Honolulu County, San Francisco, and Baton Rouge) for the Shape Up! Adults study. Whole-body DXA, anthropometry, fasting blood draw, and questionnaires (food frequency, physical activity, demographic characteristics) were completed. Linear regression was used to assess the association between HEI-2010 tertiles and VAT in all participants and age-specific strata, overall adiposity, and blood-based biomarkers while adjusting for known confounders. For the study sample, VAT, BMI, body fat percentage, total body fat, trunk fat, insulin, and insulin resistance were inversely related to diet quality (all p values < 0.004). When stratified by age, diet quality was inversely associated with VAT/SAT (subcutaneous adipose tissue) among participants 40<60 y (p < 0.008), and with VAT among participants 60<80 y (p < 0.006). Higher quality diet was associated with lower VAT, overall adiposity, and insulin resistance among this diverse sample of men and women ranging 18-80 y. More specifically, adherence to a high-quality diet may preferentially promote storage of SAT vs. VAT in adults 40<60 y, and minimize VAT accumulation in adults 60<80 y. This study was registered at clinicaltrials.gov as NCT03637855.

5.2 Introduction

Excessive abdominal adiposity is known to be more harmful than lower body adiposity [1-4]. In particular, higher levels of visceral adiposity are associated with greater risk of cardiovascular disease [5], type 2 diabetes [6,7], certain cancers [8-10] and mortality [11-13]. Determinants of visceral adipose tissue (VAT) include age [2,4,14], sex [1,2,4], physical activity [4,15], ethnicity [2,4], alcohol intake [16], and diet [4,17-19]. With advancing age, there are increases in VAT for both men and women across ethnic groups [14]. Ethnic/racial heterogeneity has been found to influence the propensity for VAT storage over subcutaneous adipose tissue (SAT) [20,21]. In the Multiethnic Cohort Adiposity Phenotype Study (MEC-APS), relative to total body fat, VAT was highest in Japanese Americans, lowest in African Americans, and intermediate for Native Hawaiians, Latinos, and whites [21]. For the effect of diet on VAT, researchers have reported higher intakes of medium-chain triglycerides, dietary fiber, calcium, and/or phytochemicals may be associated with lower VAT levels, and following a high quality dietary pattern is inversely related to VAT [17,18]. Among 1,861 participants 58-74 years of age in the MEC-APS study, results demonstrated adherence to a high quality diet (e.g., higher Healthy Eating Index-2010 (HEI-2010) score) was associated with lower adiposity, in particular VAT [18]. Studying the effects of individual foods on health is important; however, analyses using the whole diet captures the synergistic effects of nutrients on health outcomes [22]. Further research is needed to examine the effect of diet quality on VAT amongst a multiethnic group across adulthood. Given there are no official clinical guidelines for the prevention and treatment of VAT, such research may help to inform and tailor interventions targeting loss of VAT.

The primary aim of this analysis was to assess the association between diet quality as defined by the HEI-2010 score and dual X-ray absorptiometry (DXA)-based VAT among a cross-sectional sample of multiethnic adults 18-80 years of age in the US. The secondary objectives were to explore the relationships between diet quality, overall adiposity, and metabolic risk biomarkers.

5.3 Study Participants and Methods

5.3.1 Study Population

Shape Up! Adults (NIH R01 DK109008) is a cross-sectional study aiming to recruit 720 adults (ages 18-80 y) within predetermined strata by sex, age (18<40, 40<60, 60<80 y), BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), ethnicity (white, African American, Latino, Asian, Native Hawaiian, or Other Pacific Islander), and geographic location (San Francisco, CA, Baton Rouge, LA, or Honolulu County, HI). The Shape Up! Adults study began in October 2016 and the estimated completion date is September 2020. Currently, data are available for 540 participants (75% of the anticipated study sample), which was used for the current analysis. Given this is a secondary analysis, the sample size was predetermined.

Participants were recruited by convenience sampling [23] at three sites, the Pennington Biomedical Research Center (PBRC) (n = 311), University of California San Francisco (UCSF) (n=173), and University of Hawaii Cancer Center (UHCC) (n = 56) via flyers, news broadcasts, health fairs, and word of mouth. Eligible participants were identified as ambulatory individuals who met the study strata requirements. Exclusion criteria included current pregnancy, missing limbs, non-removable metal in the body (e.g., joint replacements), and a history of body-altering surgery (e.g., liposuction). Those screened as eligible over the telephone were scheduled for a clinic visit. A total of 6,943 people

responded to the study promotions. Of these, 6,403 people were excluded because they did not meet the eligibility criteria, study strata was full, or refusal to participate (Figure 5.1).

5.3.2 Study Measurements

Study preparations included fasting for at least 8 hours (water and prescription medication were allowed). Anthropometric measures, whole-body DXA, a fasting blood draw, and a characteristics questionnaire were completed in the clinic at each site. A self-administered food frequency questionnaire (FFQ) and physical activity questionnaire (PAQ) were completed at the clinic (n = 524) or at home (n = 16). As reimbursement for time and travel, each participant received a $50 gift card. Participants were provided with their whole-body DXA, BMI, and blood biochemistry panel results. All participants provided informed consent, and the study protocol was approved by the Institutional Review Boards (IRB) at PBRC (PBRC, IRB study #2017-10, FWA #00006218), UCSF (UCSF, IRB #16-20197), and the University of Hawaii Office of Research Compliance (UH ORC, CHS #24282).

Dietary data were collected using the standard format of the Diet History Questionnaire II (DHQ II) (Diet History Questionnaire, Version 2.0. National Institutes of Health, Epidemiology and Genomics Research Program, National Cancer Institute. 2010). The DHQ II is a FFQ consisting of 134 food items and 8 dietary supplement questions to capture intake in the past year and typical portion sizes [24,25]. Diet*Calc software (Diet*Calc Analysis Program, Version 1.5.0. National Cancer Institute, Epidemiology and Genomics Research Program. October 2012.), developed by the National Cancer Institute (NCI), is linked with the DHQ II Nutrient Database (DHQ Nutrient Database. dhq2.database.092914.csv. National Cancer Institute, Epidemiology and Genomics Research Program) and allows for DHQ II data to be analyzed [24]. The DHQ II Nutrient Database is comprised of information from the U.S. Department of Agriculture's (USDA) Food and Nutrient Database for Dietary Studies (FNDDS), USDA's MyPyramid Equivalents Database, and the Nutrition Data System for Research (NDS-R) [26-28]. Study staff transferred the DHQ II into Research Electronic Data Capture (REDCap), a secure web-based application for building and managing online surveys and databases, and participants completed the DHQ II online. Participants were instructed to ask study staff for assistance with the DHQ II if needed. For the small number of participants who preferred to complete the DHQ II at home, instructions were emailed on how to access and complete the DHQ II remotely. Once completed, data were downloaded from REDCap and analyzed using the Diet*Calc program for computation of total energy, nutrients, bioactive components and food groups. The Diet*Calc results file and SAS code, available through NCI [29], were used to calculate HEI-2010 total scores.

The HEI-2010 is a diet quality index and measures compliance to the 2010 Dietary Guidelines for Americans [30]. Higher HEI-2010 scores reflect greater adherence to these dietary guidelines [30]. The HEI-2010 scoring system is a 100-point scale comprised of 12 components worth 5-20 points each, including 9 adequacy components (foods to eat enough of) and 3 moderation components (foods to limit) [30]. Adequacy components include Total Fruit, Whole Fruit, Total Vegetables, Greens and Beans, Whole Grains, Dairy, Total Protein Foods, Seafood and Plant Proteins, and Fatty Acids [30]. Moderation components include Refined Grains, Sodium, and Empty Calories (kcal from solid fats, alcohol, and added sugars) [30]. The scoring system primarily uses a density based approach (i.e., per 1000 kcal), except for two components. Less than or equal to 19% of kcal is used for the Empty Calories

component and for the Fatty Acids component, a specified ratio is used for poly- and monounsaturated fatty acids to saturated fatty acids. Collectively these specified scoring mechinisms across the components allow common scoring standards to be used [31].

The Godin-Shephard leisure-time physical activity questionnaire (GSLTPAQ) was used to collect data on physical activity level [32]. Questions from the GSLTPAQ were added to the end of the online REDCap DHQ II. Briefly, the GSLPAQ consists of three questions, and asks in a typical week, how many times more than 15 minutes of strenuous, moderate, and mid/light exercise is performed [32]. Answers to the strenuous and moderate activity questions can then be used to determine if participants are insufficiently active or active. A characteristic questionnaire collected data on sex, age, and ethnicity. Participants who identified as multiple ancestries selected the ethnicity with which they identified the most.

DXA and anthropometric measures were collected using an adaptation of the protocol described by Ng et al. [33]. In the current study, two whole-body DXA scans were completed and results averaged. Each participant underwent two whole-body DXA scans with repositioning on either a Hologic Horizon/A system at UCSF or a Hologic Discovery/A system at PBRC and at UHCC (Hologic Inc., Marlborough, MA, USA). Participants were scanned according to the manufacturer's guidelines. All DXA scans were centrally analyzed at UHCC by a single certified technologist using Hologic Apex 5.5 software. Output from DXA included regional and whole-body percentage body, fat mass, lean soft tissue mass, and mean VAT and SAT for L1-L5. DXA cross calibration phantoms were circulated between all sites and calibration equations derived to remove systematic bias in all bone and soft tissue results. Anthropometric measures of waist circumference (WC) and hip circumference (HC) were collected using a flexible measuring tape according to the standard protocol from National Health and Nutrition Examination Survey (NHANES) [34]. Measurements were recorded in triplicate to the nearest 0.1 cm and results averaged. If a measurement differed by greater than 1 cm, a fourth measurement was taken and the closest three measurements averaged.

A whole blood fasting sample of 40 ml was collected from each participant. Blood samples were placed on ice and processed within 4 hours into plasma, serum, whole blood, and buffy coat components, following which they were stored at -80°C at each study site until analysis. Complete blood counts were analyzed at the respective clinic sites. Biochemical analyses of all lipid and blood chemistry profiles were performed at PBRC. Serum chemistry panels were assayed through the use of a DXC600 instrument (Beckman Coulter, Inc.; Brea, CA). Insulin was measured by immunoassay on an Immulite 2000 platform (Siemens Corporation; Washington, DC).

5.3.3 Statistical Methods

Of the 540 participants, analyses were limited to the 468 participants (men, n = 204, women, n = 264) who completed the study (excluding n = 4) with accurate DXA scans (excluding n = 36), and plausible dietary assessment information (excluding n = 32) (Figure 5.1).

Diet quality was scored using the HEI-2010 and total scores were divided into three tertiles, with the highest tertile (T3) representing the highest diet quality and the lowest tertile (T1) the lowest diet quality. Physical activity level (insufficiently active and active) was calculated using data from the GSLTPAQ, according to standard protocol [32]. Briefly, answers to questions on strenuous, and moderate exercise were multiplied by 9 and 5, respectively, and added together to obtain a total score. In order to compute a score

corresponding to health contribution, the total score was split into two groups, with a score of ≤23 representing insufficiently active, and ≥24 denoting active [32]. Forty-nine participants had missing physical activity data, and were included in analyses in a missing category.

For analysis of the primary outcome, general linear model (GLM) was used to estimate covariate-adjusted mean values for DXA-based VAT by HEI-2010 tertiles [18]. Linear trends were estimated to assess dose-response relations of VAT across HEI-2010 tertiles. The same approach was applied to analyze the data stratified by age groups (18<40, 40<60, 60<80 y) to assess if associations seen in the whole sample were present within age strata. Linear trends were also used to assess dose-response relations in VAT between age groups (18<40, 40<60, 60<80 y) within each HEI-2010 tertile. Logistic regression was applied to estimate odds ratios (OR) and 95% CI between diet quality tertiles and high VAT (>100 cm^2). This VAT cut-off was applied as previous literature has found DXA-based VAT of approximately 100 cm^2 or greater to be associated with risk of obesity-related disorders in Asian populations [35,36]. Given there is no known cutoff for high DXA-based VAT amongst a multiethnic group, additional ORs were explored with VAT cutoffs of 90 cm^2, and 110 cm^2 to 200 cm^2 in 10 cm^2 increments. GLM, linear trend between HEI-2010 tertiles, and the OR models for VAT were adjusted for age, total body fat, and total energy intake (log-transformed) as continuous variables; gender, ethnicity (white, African American, Asian, other (including NHOPI and Latino)), physical activity level (insufficiently active, active, and missing), alcohol (<14g/day, ≥14g/day of ethanol) as categorical variables [18]. Linear trends for VAT between age groups, by HEI-2010 tertiles, adjusted for the same covariates, excluding age. To evaluate effect modification by ethnicity, logistic regression was applied with an interaction term between diet quality and ethnicity.

Secondary analyses explored relationships between diet quality and anthropometric measures (BMI, WC, HC, and waist-hip ratio (WHR)), DXA-based measures (body fat percentage, total body fat, lean mass, SAT, VAT/SAT, and trunk fat), and blood based biomarkers (total cholesterol, HDL, LDL, triglycerides, glucose, insulin, HbA1c, and alanine transaminase (ALT)) applying the same methods as above. Most models were adjusted for total body fat, with the exception of models for BMI, total body fat, or body fat percentage. Participants with a missing blood or anthropometric measure were removed from the analysis for that outcome measure, and added back into the dataset for remaining analyses. Statistical significance was defined as P <0.05. Data were analyzed using IBM SPSS Statistics version 25 software (IBM Corp., Armonk, NY, USA).

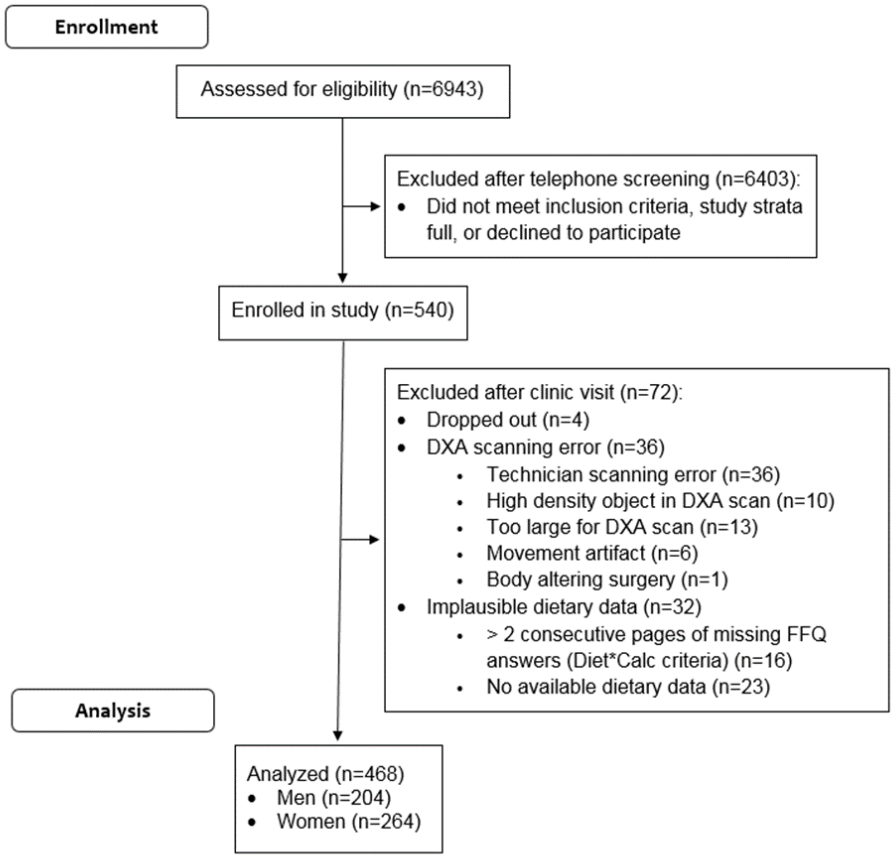

Figure 5.1 Flow diagram for the Shape Up! Adults study (NIH RO1DK109008) as of this publication.

5.4 Results

Due to the stratified recruitment, the study sample contained almost an equal number of men (43.6%) and women (56.4%) (Table 5.1) with a mean age of 45.6 ± 16.6 y. The distribution of participants in the age groups 18<40, 40<60, and 60<80 y, was 41.9%, 32.3%, and 25.9%, respectively, with the number of participants in the 18<40 y category being significantly higher than the other two age categories. Overall, 39.1% of participants identified as predominately white, 26.9% African American, 23.3% as Asian, and 10.7% as Latino or NHOPI (Latino and NHOPI recoded as other). Across age strata, the proportion of participants was similar for each ethnic group.

The mean HEI-2010 score was 67.2 ± 11.5 (range 28.9-90.3) with participants 60<80 y having significantly higher diet quality and participants 18<40 y scoring the lowest for diet quality. Consequently, the largest proportion of participants in HEI-2010 T3 (highest diet quality) were participants 60<80 y, and the largest proportion of participants in T1 (lowest diet quality) were those 18<40 y. For the whole study sample, mean VAT was 92.4 ± 58.5 cm^2, and between age group strata, participants 60<80 y had significantly higher VAT and participants 18<40 y displayed the lowest VAT.

Table 5.1 Descriptive characteristics of participants (n = 468) in the Shape Up! Adults study by age groups.

Characteristic	**All**	**18<40 y**	**40<60 y**	**60<80 y**
N, %***	468	196 (41.9)	151 (32.3)	121 (25.9)
Age, y, mean (± SD)***	45.6 ± 16.6	28.7 ± 6.2	50.9 ± 6.2	66.5 ± 4.2
Energy, kcal, median (IQR)***	1702 (1237-2452)	1838 (1359-2803)	1717 (1210-2545)	1609 (1005-1963)
VAT, cm^2, mean (± SD)***	92.4 ± 58.5	62.7 ± 38.0	109.4 ± 62.4	119.3 ± 59.8
HEI-2010, mean (± SD)***	67.2 ± 11.5	64.9 ± 10.3	66.9 ± 11.5	71.1 ± 12.1
HEI-2010, range	28.9-90.3	30.6-88.8	28.9-86.2	32.4-90.3
HEI-2010 tertile[1]				
Tertile 1 ***	156 (33.3)	80 (40.8)	44 (29.1)	32 (26.5)
Tertile 2 ***	156 (33.3)	75 (38.3)	58 (38.4)	23 (19.0)
Tertile 3 *	156 (33.3)	41 (20.9)	49 (32.5)	66 (54.5)
Sex				
Men***	204 (43.6)	92 (46.9)	60 (39.7)	52 (43.6)
Women***	264 (56.4)	104 (53.1)	91 (60.3)	69 (56.4)
Ethnicity				
White	183 (39.1)	71 (36.2)	57 (37.7)	55 (45.5)
African American	126 (26.9)	49 (25.0)	42 (27.8)	35 (28.9)
Asian	109 (23.3)	46 (23.5)	35 (23.2)	28 (23.1)
Other ***	50 (10.7)	30 (15.3)	17 (11.3)	3 (2.5)
BMI, kg/m^2				
<25	194 (41.5)	80 (40.8)	60 (39.7)	54 (44.6)
25<30 **	154 (32.9)	69 (35.2)	45 (29.8)	40 (33.1)
≥30 *	120 (25.6)	47 (24.0)	46 (30.5)	27 (22.3)
Physical activity level				
Insufficiently active	148 (32)	49 (25)	52 (34)	47 (39)
Active ***	271 (58)	135 (69)	80 (53)	56 (46)
Missing	49 (10)	12 (6)	19 (13)	18 (15)

[1] n (% column) for all such values. ***p value < 0.001 for analysis of variance between age groups (18<40, 40<60, 60<80) for quantitative variables and test of proportions for discrete variables. **p value < 0.01 for test of proportions between age groups (18<40, 40<60, 60<80). *p value < 0.05 for test of proportions between age groups (18<40, 40<60, 60<80). VAT: visceral adipose tissue. HEI-2010: Healthy Eating Index-2010.

For the study sample, BMI, body fat percentage, total body fat, VAT, and trunk fat were inversely related to diet quality, with a significant trend across tertiles (Table 5.2). Within age groups; for participants 18<40 y, BMI, body fat percentage, total body fat, SAT, and trunk fat were inversely related to diet quality with a significant trend across tertiles. Unique to participants 40<60 y, VAT/SAT was inversely related to diet quality, with a significant trend across tertiles. For participants 60<80 y, BMI, body fat percentage, total body fat, and VAT were inversely related to diet quality with a significant trend across tertiles. Between age groups; among those with the highest diet quality, participants 18<40 y had significantly lower WC, WHR, body fat percentage, VAT, VAT/SAT, and trunk fat (Table 5.2) compared to participants 60<80 y, and the trend was significant across age groups. Also, among T3 participants 18<40 y, HC and lean mass was significantly higher compared to participants 60<80 y, with a significant trend across age groups. These patterns were similar among participants in T2 and T1, with the exception of body fat percentage for participants in T2, which did not significantly differ across age groups.

For the study sample, participants with the highest diet quality had an OR of 0.39 (95% CI 0.25-0.62) for high VAT (defined as VAT over 100 cm^2) compared to participants with the lowest diet quality ($p = 0.04$). The interaction with ethnicity in this model was not significant ($p = 0.31$). For the analysis of ORs with VAT cutoffs ranging from 90 cm^2 to 200 cm^2 in increments of 10 cm^2, the lowest OR for T3 vs. T1 was 0.19, which corresponded to a VAT cutoff of 110 cm^2. The odds of high VAT was significantly lower for participants in T3 compared to T1 for almost all VAT cutoffs except the VAT cutoffs of 140 cm^2, 150 cm^2, and 180 cm^2, where the ORs were not significant.

For blood-based biomarkers (Table 5.3) among the total study sample, higher diet quality was inversely related to insulin and insulin resistance, with a significant trend across tertiles. Among participants 18<40 y and those 40<60 y, higher diet quality was inversely related to insulin and insulin resistance, with a significant trend across tertiles. Unique to participants 18<40 y were the significantly lower triglycerides for T3 compared to T1 with a significant trend.

Table 5.2 Adjusted means (95% CI) for body measurements by Healthy Eating Index-2010 tertiles and age groups.

Body measure[1]	**HEI-2010 Tertiles**	**All (*n* = 468)**		**18<40 y (*n* = 196)**		**40<60 y (*n* = 151)**		**60<80 y (*n* = 121)**		***p*-trend**[2]
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
BMI, kg/m^2	T1	27.5	26.0-29.0	26.4	24.5-28.2	28.9	24.6-33.1	28.3	25.5-31.1	0.212
	T2	27.6	26.0-29.0	26.2	24.4-28.0	29.8	26.1-33.5	25.6	22.7-28.6	0.547
	T3	24.6	23.0-26.2	23.9	21.4-26.5	24.8	20.9-28.6	25.0	22.6-27.4	0.922
	p-trend[3]	0.002[4,5]		0.049[5]		0.110[4]		0.010[5]		
WC, cm[6]	T1	93.1	91.9-94.4	88.6	86.9-90.3	98.2	95.5-100.9	94.8	91.3-98.3	0.048[7]
	T2	92.4	91.2-93.6	88.8	87.1-90.5	95.1	92.7-97.4	95.2	91.4-98.9	0.028[7]
	T3	92.6	91.3-94.0	88.6	86.2-91.0	96.8	94.4-99.3	94.4	91.3-97.6	0.039[7]
	p-trend	0.542		0.987		0.401		0.825		
HC, cm[6]	T1	102.4	101.4-103.4	101.8	100.2-103.4	105.2	103.3-107.1	100.8	98.4-103.1	0.011[7]
	T2	102.5	101.6-103.5	101.7	100.0-103.3	105.1	103.5-106.8	101.8	99.3-104.3	0.020[7]
	T3	103.0	101.9-104.1	102.3	100.0-104.5	104.9	103.2-106.6	102.2	100.1-104.2	<0.001[7,8]
	p-trend	0.307		0.644		0.773		0.209		
WHR[6]	T1	0.91	0.90-0.92	0.87	0.85-0.89	0.93	0.91-0.96	0.94	0.90-0.98	0.001[7]
	T2	0.90	0.89-0.92	0.88	0.86-0.90	0.91	0.88-0.93	0.94	0.90-0.98	0.020[7]
	T3	0.90	0.88-0.91	0.87	0.84-0.89	0.92	0.89-0.95	0.93	0.89-0.96	<0.001[7]
	p-trend	0.134		0.835		0.441		0.417		
% body fat	T1	29.1	27.8-30.4	26.9	24.9-28.9	29.3	26.7-32.0	31.5	28.1-34.9	0.002[7]
	T2	28.5	27.2-29.8	25.6	23.6-27.6	31.3	28.9-33.6	27.7	24.1-31.4	0.092
	T3	25.9	24.5-27.3	23.3	20.7-26.0	26.7	24.3-29.1	27.6	24.6-30.6	0.013[7]
	p-trend	<0.001[4,5]		0.008[5]		0.098[4]		0.014[5]		
Total body fat, kg	T1	22.9	20.9-24.9	20.1	17.1-23.1	24.3	19.9-28.7	24.6	19.9-29.3	0.082
	T2	22.1	20.1-24.0	19.1	16.1-22.1	25.6	21.8-29.4	19.6	14.6-24.6	0.979
	T3	18.4	16.3-20.6	15.8	11.7-19.9	20.1	16.1-24.0	19.1	14.9-23.2	0.322
	p-trend	<0.001[4,5]		0.033[5]		0.107[4]		0.011[5]		
Lean mass, kg	T1	54.3	53.1-56.0	54.6	52.2-57.1	57.2	54.6-59.8	52.2	49.0-55.4	0.035[7]
	T2	54.7	53.3-56.2	56.1	53.7-58.6	55.4	53.1-57.7	51.6	48.1-55.0	<0.001[7]
	T3	55.3	53.7-56.9	54.7	51.3-58.1	57.8	55.4-60.2	53.0	50.2-55.9	0.009[7,8]
	p-trend	0.414		0.978		0.714		0.569		
SAT, cm^2	T1	296	287-304	272	260-284	314	296-333	308	288-329	0.980
	T2	295	287-303	271	259-282	318	302-334	311	289-333	0.191
	T3	288	280-297	255	239-272	326	309-343	299	281-317	0.465
	p-trend	0.168		0.037[5]		0.292		0.332		
VAT, cm^2	T1	101	95-108	68	61.4-74.6	119	104-134	138	120-155	<0.001[7,8]

	T2	96	90-102	63	56.0-69.2	117	104-131	117	98-136	<0.001[7]
	T3	87	80-94	60	51.3-69.5	104	89-118	115	99-131	<0.001[7,8]
	p-trend	0.001[4,5]		0.089		0.100		0.006[5]		
VAT, cm[3]	T1	529	495-563	354	320-389	620	541-700	718	627-810	<0.001[7,8]
	T2	500	467-533	326	292-361	611	541-681	609	511-707	<0.001[7]
	T3	455	419-492	315	267-362	541	467-614	600	518-681	<0.001[7,8]
	p-trend	0.001[4,5]		0.089		0.100		0.006[5]		
VAT, g	T1	489	458-521	328	296-360	574	500-647	665	580-749	<0.001[7,8]
	T2	462	432-493	302	270-333	565	500-630	563	472-654	<0.001[7]
	T3	421	387-455	291	247-335	500	432-568	555	479-630	<0.001[7,8]
	p-trend	0.001[4,5]		0.089		0.100		0.006[5]		
VAT/SAT	T1	0.4	0.3-0.4	0.3	0.2-0.3	0.4	0.4-0.5	0.4	0.4-0.5	<0.001[7]
	T2	0.4	0.3-0.4	0.3	0.2-0.3	0.4	0.4-0.5	0.4	0.3-0.5	<0.001[7]
	T3	0.3	0.3-0.4	0.3	0.3-0.4	0.3	0.3-0.4	0.4	0.4-0.5	<0.001[7,8]
	p-trend	0.235		0.230		0.008[4,5]		0.571		
Trunk fat, kg	T1	10.8	10.5-11.1	9.4	9.0-9.7	12.0	11.5-12.7	11.8	11.1-12.4	0.009[7]
	T2	10.5	10.3-10.8	9.1	8.8-9.5	11.7	11.2-12.2	11.4	10.7-12.1	0.002[7]
	T3	10.3	10.0-10.6	8.9	8.5-9.4	11.7	11.1-12.2	11.2	10.7-11.8	<0.001[7]
	p-trend	0.004[5]		0.052[5]		0.258		0.096		

[1]General linear models (GLM) used to obtain adjusted means including adjustment for gender, race, physical activity level (PAL), age, alcohol, total energy intake, and total body fat. GLM for BMI, percentage body fat, and total body fat did not include adjustment for total body fat. [2]GLM used to obtain trend by HEI-2010 tertiles between age groups including adjustment for gender, race, PAL, alcohol, total energy intake, and total body fat. Trend test for BMI, percentage body fat, and total body fat did not include adjustment for total body fat. [3]GLM used to obtain trend by age groups between tertiles; including adjustment for gender, race, PAL, age, alcohol, total energy intake, and total body fat. Trend test for BMI, percentage body fat, and total body fat did not include adjustment for total body fat. [4]Significant difference by GLM between HEI-2010 tertile 3 and HEI-2010 tertile 2. [5]Significant difference by GLM between HEI-2010 tertile 3 and HEI-2010 tertile 1. [6]Missing values: 4 for waist circumference, hip circumference, and waist hip ratio. [7]Significant difference by GLM between 60<80 and 18<40. [8]Significant difference by GLM between 60<80 and 40<60. SAT: Subcutaneous adipose tissue. VAT: Visceral adipose tissue. WC: Waist circumference. WHR: Waist/hip ratio. HC: Hip circumference.

Table 5.3 Adjusted means (95% CI) for blood-based biomarkers by Healthy Eating Index-2010 (HEI-2010) tertiles and age groups.

Blood-based biomarker[1,2]	**HEI-2010 Tertiles**	**All**		**18<40 y**		**40<60 y**		**60<80 y**	***p*-trend[3]**	
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
HbA1c, %	T1	5.4	5.3-5.5	5.1	5.0-5.3	5.6	5.3-5.9	5.6	5.4-5.9	<0.001[4]
	T2	5.5	5.3-5.6	5.2	5.1-5.3	5.5	5.3-5.8	5.7	5.4-6.0	0.008[4]
	T3	5.3	5.2-5.4	5.1	5.0-5.3	5.3	5.0-5.6	5.6	5.3-5.9	<0.001[4,5]
	p-trend[6]	0.111[7]		0.850		0.063		0.722		
Insulin, uU/mL	T1	13.0	11.6-14.5	11.3	9.4-13.1	14.7	12.0-17.5	14.7	10.2-19.1	0.177
	T2	10.4	9.0-11.8	9.1	7.3-10.9	9.9	7.5-12.3	14.1	9.3-18.9	0.074
	T3	9.2	7.6-10.7	7.8	5.3-10.3	8.5	6.0-11.1	12.4	8.5-16.3	0.004[4,5]
	p-trend	0.000[8]		0.005[8]		<0.001[8]		0.275		
HOMA-IR	T1	3.1	2.7-3.5	2.4	2.0-2.9	3.6	2.8-4.3	3.7	2.3-5.2	0.021[4]
	T2	2.6	2.2-3.0	2.0	1.6-2.4	2.5	1.8-3.1	3.7	2.2-5.3	0.022[4]
	T3	2.1	1.6-2.5	1.6	1.0-2.2	1.9	1.2-2.5	3.1	1.8-4.4	0.001[4,5]
	p-trend	<0.001[8]		0.005[8]		<0.001[8]		0.333		
Glucose, mg/dL	T1	93.2	89.7-96.7	86.4	83.0-89.7	96.2	88.4-104.1	97.4	85.6-109.3	0.034[4]
	T2	95.8	92.3-99.2	86.4	83.0-89.8	99.3	92.4-106.2	103.8	91.0-116.5	0.008[4]
	T3	90.5	86.8-94.3	82.2	77.5-86.9	90.9	83.7-98.2	99.5	88.9-110.0	<0.001[4,5]
	p-trend	0.230[7]		0.075		0.266[7]		0.715		
ALT, umol/L	T1	25.9	23.5-28.3	24.8	20.3-29.4	25.4	21.8-29.0	25.9	21.0-30.9	0.773
	T2	23.3	21.0-25.7	20.2	15.6-24.7	26.2	23.0-29.4	22.9	17.5-28.1	0.820
	T3	24.1	21.5-26.7	21.2	14.9-27.5	26.6	23.3-30.0	23.9	19.5-28.3	0.752
	p-trend	0.238		0.241		0.578		0.377		
Cholesterol, mg/dL	T1	188.9	180.8-197.1	178.2	167.4-189.1	196.2	180.8-211.5	183.5	158.6-208.5	0.401
	T2	193.4	185.3-201.4	180.8	169.9-191.6	203.3	189.8-216.8	192.1	165.3-218.8	0.363
	T3	190.1	181.3-199.0	174.1	159.0-189.2	200.0	185.8-214.2	198.9	176.7-221.0	0.017[4]
	p-trend	0.815		0.578		0.681		0.194		
HDL, mg/dL	T1	59.2	56.5-61.9	54.1	50.0-60.0	62.5	57.2-67.9	62.0	54.8-69.1	0.010[4]
	T2	61.9	59.2-64.5	60.6	56.7-64.6	62.1	57.5-66.8	63.7	56.0-71.3	0.622
	T3	59.9	57.0-62.8	55.9	50.4-61.4	64.5	59.6-69.4	60.9	54.5-67.2	0.297[5]
	p-trend	0.658		0.493		0.540		0.741		
LDL, mg/dL	T1	110.5	104.4- 117.0	109.5	100.9-118.2	111.0	99.0-123.1	105.2	85.1-125.4	0.984
	T2	111.6	105.3-118.0	106.0	97.4-114.6	118.4	107.7-129.1	106.0	84.4-127.6	0.733[5]
	T3	111.5	104.6-118.5	106.6	94.7-118.5	113.2	102.1-124.4	118.0	100.1-135.9	0.081

	p-trend	0.805		0.611		0.763		0.180		
TG, mg/dL	T1	108.0	95.7-120.2	103.9	86.4-121.3	110.8	82.7-138.9	104.1	75.3-132.9	0.977
	T2	99.3	87.2-111.3	88.6	71.2-106.1	102.8	78.0-127.5	106.2	75.4-137.1	0.158
	T3	95.7	82.5-108.9	80.0	55.9-104.2	103.7	77.7-129.8	97.7	72.2-123.2	0.021[4]
	p-trend	0.114		0.045[8]		0.681		0.637		

[1]General linear models (GLM) used to obtain adjusted means including adjustment for gender, race, physical activity level (PAL), age, alcohol, total energy intake, and total body fat. [2]Missing values: 4 for alanine transaminase, cholesterol, HDL, and glucose; 5 for triglycerides and HbA1c; 9 for LDL, and 8 for insulin and HOMA-IR. [3]GLM used to obtain trend by HEI-2010 tertiles between age groups; including adjustment for gender, race, PAL, alcohol, total energy intake, and total body fat. [4]Significant difference by GLM between 60<80 and 18<40. [5]Significant difference by GLM between 60<80 and 40<60.[6]GLM used to obtain trend by age groups between tertiles; including adjustment for gender, race, PAL, age, alcohol, total energy intake, and total body fat. [7]Significant difference by GLM between HEI-2010 tertile 3 and HEI-2010 tertile 2. [8]Significant difference by GLM between HEI-2010 tertile 3 and HEI-2010 tertile 1.TG: Triglycerides. ALT: Alanine transaminase.

5.5 Discussion

In this cross-sectional analysis of multiethnic adults, diet quality for the whole sample was inversely related to VAT, overall adiposity, insulin, and insulin resistance. Among participants 40<60 y, VAT/SAT was inversely related to diet quality, and among participants 60<80 y, VAT was lower for participants with the highest diet quality compared to the lowest diet quality. These results suggest following a higher quality diet may help to minimize VAT accumulation in adults 18-80 y, in particular adults 60<80 y. In addition, following a higher diet quality may help to preferentially promote storage of SAT vs. VAT in adults 40<60 y. Participants 60<80 y had higher VAT/SAT, VAT, overall adiposity, and blood-based biomarkers for metabolic risk, than participants 18<40 y. Despite the effect of aging on VAT, diet quality appears to limit these effects.

Differences in VAT levels by ethnicity [20,21] and by age [2,4,14] have previously been explored. The current analyses are novel as they include multiethnic participants with a wide age range, spanning 18-80 y. Splitting the sample by VAT of 100 cm^2, a cut off for high risk of obesity-related disorders [35,36], demonstrated that those with higher diet quality may have lower odds of poor metabolic outcomes than those with lower quality diets. This hypothesis is supported by the inverse relationship between diet quality, insulin and insulin resistance.

The significant association found between diet quality and VAT for participants 60<80 y is consistent with results from the MEC-APS (average age 69.2) [18]. To our knowledge, no published study has explored the relationship between VAT/SAT and diet quality among a younger multiethnic population. Thus, the results reported here may represent the first time a significant association has been reported among men and women 40<60 y. In this current analysis, participants 40<60 y in T3 (i.e., highest diet quality) had lower VAT and higher SAT compared to participants in T1, although these differences were not significant, probably due to the limited sample size. In comparison, in the Framingham Heart Study, among a larger sample of 2,926 participants with a mean age of 50 ± 10 y, a significant inverse relationship was found between diet quality and VAT [37]. The non-significant relationship between diet quality and VAT, for participants 18<40 y, may be due to their relatively low levels of VAT.

In this current study, an inverse relationship was found between diet quality and BMI, body fat percentage, and total body fat. These results are consistent with those found in MEC-APS with diet quality being inversely associated with BMI and total body fat [18]. Previous literature has reported that WC is highly correlated with abdominal adiposity, even more so than BMI [38,39]. In this current study, an inverse association was seen between diet quality, VAT, and BMI but not for WC. A systematic review of waist measurement sites for determining central adiposity highlighted that WC measures were more strongly correlated with VAT for men vs. women, and white vs. Asian adults [40]. Consequently, the sex and ethnicity mix of this current study sample may explain the null relationship between diet quality and WC.

Diet quality among participants in this study appears to be higher than in the wider US population. Mean HEI-2010 scores for participants 18<40, 40<60, and 60<80 y were 64.9, 66.9, and 71.1, respectively. According to the 2015 Dietary Guidelines Advisory Committee Report, the average HEI-2010 scores for people 19-30, 31-50, 51-70, and ≥71 y in the US were 50.5, 57.4, 61.6, and 65.8, respectively [41]. Participants in this current study were recruited by stratified

sampling, which may explain the differences in these HEI-2010 scores. Similar to this current study, MEC-APS participants were recruited from Hawaii and Los Angeles through stratified sampling and comprised of; white, African American, Native Hawaiian, Japanese American, and Latino participants. The age range of MEC-APS participants was 60-77 years and the mean HEI-2010 score was 72.7 [18]. These results closely match the 71.1 HEI-2010 score among the participants in the 60<80 y group in this current study. MEC-APS participants completed a FFQ validated for use among multiethnic populations that include Japanese-Americans [42]; whereas, the DHQ II FFQ has yet to be validated for Asian Americans [43-45]. The positive linear association between HEI-2010 scores and age in this current study is consistently seen in the literature among multiethnic groups [18,46]. This evidence supports the reliability of using the DHQ II for collection of dietary data among multiethnic populations, including Asian Americans.

A strength of this study was the inclusion of DXA-based VAT measures. Computed tomography (CT) and MRI are considered the "gold standards" for measurement of VAT [47-49]. However, DXA-based VAT strongly correlates with CT and DXA can be performed with lower exposure of radiation to both the participant and examiner [49,50]. Additional strengths were the inclusion of an ethnic diverse population of adults 18-80 y, adjusting for known confounders, and the use of the criterion validated HEI-2010 dietary index for the assessment of diet quality [51]. A limitation was the sample size, which did not allow for stratification by sex and ethnicity. In addition, being a cross-sectional study, a causal relationship between diet quality and VAT cannot be derived. Due to the stratified recruitment, and convenience sampling, results of this study may not be representative of the US population [23]. The study size limited how many variables could be controlled for. Therefore, other factors not controlled for may have affected study results, e.g., smoking status, pharmacological agents, and menopausal status [4]. Previous research found that the DHQ underestimates energy and protein intake [52]; however, all participants were subjected to this bias. Administering the DHQ II through REDCap may have changed the user experience when completing the DHQ II; consequently, results may not align with previous validation of the DHQ. However, associations found between diet quality and VAT were as expected.

In conclusion, despite the influence of sex, ethnicity and age on VAT, higher quality diet was associated with lower VAT, overall adiposity, and improved metabolic risk biomarkers, especially insulin and insulin resistance, amongst a multiethnic group ranging 18-80 y of age. In particular, following a higher quality diet may help to preferentially promote storage of SAT vs. VAT in adults 40<60 y and minimize VAT accumulation in adults 60<80 y. These results also highlight the importance of adults adhering to the 2010 Dietary Guidelines for Americans to help optimize health outcomes.

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CHAPTER 6. CONCLUSIONS

Findings from this dissertation demonstrate that following a healthy dietary pattern is associated with lower visceral adipose tissue (VAT), and a reduced risk of mortality from all-causes, cardiovascular disease (CVD), and cancer. In particular, intermittent energy restriction combined with a Mediterranean (IER+MED) diet, may help to lower VAT, and improve liver function. This is important given VAT is a risk factor for chronic disease and mortality, and the high prevalence of chronic disease in the US. Currently, there are no clinical guidelines for the prevention and management of VAT; therefore, this dissertation may help to build the evidence base needed to develop such guidelines.

This chapter, Conclusions, will provide the aims, a summary, the limitations, and future directions for each of the three studies that make up this dissertation.

6.1 Study One, Testing the Predictive Validity of the Healthy Eating Index-2015 in the Multiethnic Cohort: Is the Score Associated with a Reduced Risk of All-Cause and Cause-Specific Mortality?

6.1.1 Aim

The aim of this study was to examine the association between the Healthy Eating Index-2015 (HEI-2015) and mortality from all-cause, CVD, and cancer in the Multiethnic Cohort (MEC), which represents a large cohort of adult men and women from five distinct ethnic groups residing in Hawaii and Los Angeles (LA).

6.1.2 Summary

This analysis of diet quality (HEI-2015 scores) and mortality outcomes among the MEC, demonstrates that closer compliance to the Dietary Guidelines for Americans (DGAs) 2015–2020 is associated with a lower risk of mortality from all-cause, CVD, and cancer. Comparing those with the lowest quality diets (lowest HEI-2015 scores) to those with the highest quality (highest HEI-2015 scores), the reduction in risk of mortality from all-cause, CVD, and cancer was 21%, 24%, and 20%, respectively, for men and 21%, 25%, and 16%, respectively, for women. This study also reinforced the multidimensionality of the HEI and the representation of diet quality using a wide array of components. For example, removing one HEI component at a time from the survival analysis did not change the protective association of the remaining HEI components. Supporting the index goal of no one HEI component making a significant independent contribution to the total HEI-2015 score. This analysis also highlighted dietary changes that may help improve mortality outcomes for MEC participants with the lowest quality diets. The components with the most substantial differences in median scores between quintile 1 (lowest quality diets) and quintile 5 (highest quality diets) were identified as Total Fruits, Whole Fruits, Greens and Beans, Whole Grains, and Refined Grains for men and Total Fruits, Whole Grains, and Refined Grains for women. Also, the components with the lowest median scores were the same for people in quintile 1 and quintile 5. These components were Dairy, Fatty Acids, and Sodium, with median scores

of less than 50%. Therefore, improving the intake of foods that fall into these components may help to reduce mortality risk.

6.1.3 Limitations

A limitation of this study was the use of a FFQ to collect dietary information at baseline, which could introduce bias, for example misreporting of dietary intake or foods often consumed not being available on the FFQ [1]. However, this FFQ was validated and calibrated in each ethnic-sex group, and the correlations between the FFQ and 24-hour dietary recalls were 0.55–0.74 for energy adjusted nutrients [1]. Another limitation was dietary data only being assessed once at baseline; therefore, this analysis was not able to capture the influence of dietary changes on mortality outcomes. Also, all demographic and anthropometric variables were self-reported, and we cannot rule out whether other factors not measured and controlled for, could have affected mortality outcomes; e.g., access to health care. Participants in the MEC were recruited from Hawaii and Los Angeles (LA); therefore, results of this study may not be generalizable outside of these areas.

6.1.4 Future Directions

In this study, the relationship between HEI-2015 scores and mortality outcomes was primarily explored for the whole study sample completing the FFQ. In a secondary analysis, where mortality outcomes were split by ethnicity, it was found that Native Hawaiian men and women had a null association between HEI-2015 quintile 1: quintile 5 and all-cause, CVD, and cancer mortality. Also, Latino men and women had null associations between HEI-2015 quintile 1: quintile 5 and CVD mortality. These null associations may be due to the relatively smaller sample size of Native Hawaiians in the MEC, and the low rate of CVD mortality among Latinos. However, future analyses among the MEC could further explore the relationship between HEI-2015 scores, HEI-2015 component scores, and mortality by ethnic group. These analyses may help to assess whether HEI indices, and the DGAs, require additional tailoring based on ethnicity.

6.2 Study Two, Effects of Intermittent Energy Restriction Combined with a Mediterranean Diet on Reducing Visceral Adiposity: A Randomized Active Comparator Pilot Study

6.2.1 Aim

The primary aim of the present study was to finalize and implement a protocol for an intermittent energy restriction (IER) intervention to evaluate the effectiveness of a culturally adapted IER and MED combined diet (IER+MED) to reduce VAT among East Asian Americans. Secondary aims were to evaluate study retention and protocol adherence, and changes in total adiposity and metabolic risk biomarkers.

6.2.2 Summary

The Healthy Diet and Lifestyle Study (HDLS) is the first known pilot study to evaluate the effectiveness of a culturally adapted IER+MED vs. an active comparator (DASH diet) to reduce DXA measured VAT among East Asian Americans. Both study groups had significant reductions in VAT, weight, and total adiposity. Although loss of VAT was higher

in IER+MED than in DASH, this appeared to be due to the greater loss of total fat in IER+MED as there was no significant group difference after adjusting for concurrent total fat mass. The reduction in ALT was significantly greater in IER+MED vs. DASH, a difference maintained after adjusting for concurrent total fat mass. This indicates a potential benefit of IER+MED on liver function. Overall, this pilot study demonstrated that an IER+MED vs. DASH intervention could be successfully conducted with East Asian Americans, and with a low attrition rate of 10%. The low attrition rate may have been due to the use of the mFR™ to collect dietary information, which could have helped limit participant burden when completing a food record. Also, the use of motivational interviewing, and conducting participant follow-up calls over the telephone, may have helped to provide a supportive and flexible environment for participants, and contributed to the low attrition rate.

6.2.3 Limitations

Limitations of the HDLS pilot include the small sample size, which may have limited statistical power to show small differences between groups. Also, the possible misreporting of dietary intake, with underreporting of dietary intakes being common among people with overweight or obesity [2,3]. However, weight loss achieved by participants in the IER+MED and DASH groups corresponded well to the average change in daily energy intake between baseline and Week 11, indicating at the group level, the dietary data was collected and analyzed accurately [4,5]. Another limitation is that results from the 6-month post-intervention telephone interview may not be representative of the study sample due to not all participants responding and the self-reported nature of the information collected. There have been limited studies comparing DXA-based VAT measures with CT or MRI and, in the few studies reported, the DXA results overestimated VAT, particularly in individuals with higher VAT levels [6-8].

6.2.4 Future Directions

The results of HDLS are very promising. However, given this was a pilot study, and IER+MED is a novel area of research, there are many opportunities to build and expand on this research. For example, in HDLS, visceral adiposity, as well as total fat mass and alanine transaminase (ALT), were reduced to a greater extent in the IER+MED diet group than in the DASH diet group, possibly because the observed decrease in energy intake was greater in the IER+MED group. Future trials could be conducted where the energy deficit prescribed is the same for the IER+MED and active comparator groups. This would help to examine if it is energy restriction or specifically intermittent energy restriction influencing changes in health outcomes. Also, changes in VAT in the IER+MED group may have resulted from following a high protein low carbohydrate diet on restricted days, following a Mediterranean diet on non-restricted days, energy restriction, or a combination of these factors. Future IER+MED trials could include three studies arms being; IER+MED, euenergetic MED diet, or a continuous energy restricted MED diet to help determine whether the IER days, MED days, energy restriction, or a combination of these exposures effect changes in health outcomes.

The greater improvement in ALT in the IER+MED group vs. the DASH group is important as ALT is a biomarker for non-alcoholic fatty liver disease (NAFLD) [9]. This highlights the potential benefit of IER+MED on liver function. However, liver fat measurement, e.g., by abdominal magnetic resonance imaging (MRI) scans, are needed to

confirm this. Given MRI are expensive and time-consuming to administer, research in this area could work towards developing less expensive methods for measuring liver fat and other ectopic fat stores, e.g., biomarkers and DXA-based measures for liver fat.

Another area for future exploration is comparing the effect of consecutive vs. non-consecutive IER days in IER+MED trials on VAT. The HELENA trial incorporated two days of IER per week, over 50 weeks, to assess the effects of IER on VAT [10]. This trial found that IER did not exert stronger effects on VAT loss than CER [10]; however, their trial incorporated two non-consecutive restriction days. Incorporating two consecutive vs. non-consecutive restriction days may have differing effects on health outcomes. The former may likely produce higher reductions on insulin resistance and percentage body fat [10,11].

Given HDLS was a pilot study, the sample size was small and did not allow for stratification of analyses by sex. Therefore, further studies addressing a larger sample, with separate analyses for men and women, are needed to confirm the effectiveness of the IER+MED diet on change in VAT, and its possible beneficial effect on liver fat, in the short term and long term.

6.3 Study Three, Diet Quality is Associated with Lower Visceral and Overall Adiposity Among a Multiethnic Adult Population

6.3.1 Aims

The primary aim of this cross-sectional study was to assess the association between diet quality as defined by the Healthy Eating Index-2010 (HEI-2010) score and dual X-ray absorptiometry (DXA)-based VAT among multiethnic adults 18-80 years of age in the US. The secondary objectives were to explore the relationships between diet quality, overall adiposity, and metabolic risk biomarkers.

6.3.2 Summary

In this cross-sectional analysis of multiethnic adults in the Shape Up! Adults study, diet quality (HEI-2010 scores) for the whole group was inversely related to VAT, overall adiposity, insulin, and insulin resistance. Among participants 40<60 y, VAT/SAT was inversely related to diet quality, and among participants 60<80 y, VAT was lower for participants with the highest diet quality compared to the lowest diet quality. These results suggest following a higher quality diet may help to minimize VAT accumulation in adults 18-80 y, in particular adults 60<80 y. Also, following a higher diet quality may help to preferentially promote storage of SAT vs. VAT in adults 40<60 y. Participants 60<80 y had higher VAT, subcutaneous adipose tissue (SAT), VAT/SAT, overall adiposity, and blood-based biomarkers for metabolic risk than participants 18<40 y. Despite the effect of aging on VAT, diet quality appears to limit these effects.

6.3.3 Limitations

A limitation of this study was the sample size, which did not allow for stratification by sex and ethnicity. Also, being a cross-sectional study, a causal relationship between diet quality and VAT cannot be derived. Due to the stratified recruitment, and convenience sampling, results of this study may not be representative of the US population [12]. Also,

other factors not controlled for may have affected study results, e.g., smoking status, pharmacological agents, and menopausal status [13]. Previous research found that the Diet History Questionnaire (DHQ) underestimates energy and protein intake [14]; however, all participants were subjected to this bias. Administering the DHQ II through REDCap may have changed the user experience when completing the DHQ II; consequently, results may not align with previous validation of the DHQ. However, associations found between diet quality and VAT were as expected.

6.3.4 Future Directions

The small sample size of this cross-sectional study did not allow for stratification of analyses by sex, and ethnicity, and limited the number of confounders that could be controlled for. The National Health and Nutrition Examination Survey (NHANES) has a substantially larger sample size, and provides data on diet quality [15] as well as DXA-based VAT measures [16]. VAT data is yet to be released; however, once available, NHANES data could be used to analyze the association between diet quality and VAT. These analyses could be stratified by sex and ethnicity, and adjust for an extensive number of confounders. This research may help provide further evidence in support of following a high quality diet to reduce VAT, and rationale for funding cohort and RCT studies in this area of research. Ultimately the aims are to build enough scientific evidence to determine causality between diet quality and VAT, and to develop clinical guidelines for the prevention and management of VAT.

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APPENDICIES

APPENDIX A. Key papers reviewed for this dissertation

Methods for collecting dietary intake data: mFR and FFQ studies central to this dissertation.			
mFR studies among adults			
Study	Population	Objective/s	Conclusion/s
Daugherty et al (2012)[1]	Adolescents (n=78) and adults (n=57), aged 11-65 years, West Lafayette, Indiana, USA	Evaluate skills required to complete a mFR, and perceptions and preferences when completing a mFR	-Majority of adults and adolescents had the skills to complete a mFR -Interactive training is necessary before completing mFR in community dwelling settings - Findings will help with age-specific development of the mFR
Bathgate et al (2017)[2]	Adolescents and young adults without Down syndrome (n= 244, aged 18-30 years), or with Down syndrome (n=58, aged 12–30 years), Perth, Western Australia.	Assess the usability of the mFR among adolescents and young adults with Down syndrome	-The mFR shows great promise as a feasible method of assessing diet in adolescents and young adults with Down syndrome.
Boushey et al (2017)[3]	Men and women (n=45, aged 21–65 years), West Lafayette, Indiana, USA	Test the accuracy of the mFR by comparing reported energy intake (rEI) to total energy expenditure (TEE) using the doubly labeled water (DLW) method. Usability was also assessed.	-The accuracy of the mFR is comparable to traditional dietary records and other image-based methods. - The mFR was received well and usability was rated as easy
The Multiethnic Cohort (MEC) FFQ and the Diet History Questionnaire II (DHQ-II) FFQ			
Study	Population	Objective/s	Conclusion/s
Stram et al (2000)[4]	African-Americans (n=775), Japanese-Americans (n=769), Latinos (n=649), 850 whites (n=850), men and women (aged 45-75 years), from Hawaii and Los Angeles apart of the Multiethnic Cohort study.	Assess the performance of the dietary questionnaire used in a multiethnic cohort in a calibration substudy that compared diet reported from the questionnaire with 24-hour dietary recalls	Calibration and correlation results for nutrient densities and energy corrected nutrients were comparable with those reported by other groups, and highly satisfactory for energy-adjusted nutrients for all subgroups.
Subar et al (2001)[5]	Men and women (n=1,640, aged 20-70 years) from a nationally representative sample in the USA.	Validate and compare the DHQ with the Block and Willett FFQs	The DHQ and the Block FFQ are better at estimating absolute intakes than the Willett FFQ, but after energy adjustment, all three are comparable for purposes of assessing diet-disease risk.
Thompson et al (2002)[6]	Men and women (n=623, aged 25 to 70 years) from Washington, DC, USA.	Testing changes in a FFQ on the basis of cognitive theory and testing results in greater accuracy	Accuracy of FFQ reporting can be improved by restructuring questions based on cognitive theory and testing
Subar et al (2003)[7]	Men and women (n=484, aged 40–69 years) from Montgomery County, Maryland, USA.	Assess dietary measurement error using the FFQ, the 24-hour dietary recall (24HR), doubly labeled water and urinary nitrogen.	A greater percentage of men and women under-reported energy and protein intake when completing a FFQ vs. 24HR. Also, underreporting of total amount of energy and protein consumed was greater when completing the FFQ vs. 24HR.

Examining diet using dietary patterns:				
Mediterranean-style diet				
Study	Population	Objective/s	Dietary pattern examined	Conclusion/s
de Lorgeril et al (1994)[8]	Men and women, (n= 605, less than 70 years of age), in The Lyon Diet Heart Study, France.	Assess the effects of the Lyon Diet Heart Study, which is a prospective, randomized, single-blinded, multi-clinic, secondary prevention trial aimed at reducing the risk of cardiovascular deaths by diet modification and recurrent myocardial infarction in survivors of a first myocardial infarction. Follow-up time 5 years. Follow-up time of this intermediate analysis was 27 months.	Patients were randomly assigned to the experimental or control group. Experimental group were advised to follow a Med-type diet.	This intermediate analysis at 27 months of follow-up, demonstrated that the Mediterranean diet was more efficient than the control diet in secondary prevention of coronary events and death.
Trichopoulou et al (1995)[9]	Men and women (n=182, more than 70 years old) across three Greek villages.	To assess the influence of a specific dietary pattern (MED) on overall survival.	An a priori index on the basis of eight component characteristics of the traditional common diet in the Mediterranean region.	An a priori defined nutritional pattern which closely reflects the Greek version of the Mediterranean diet favorably affects life expectancy among elderly people
de Lorgeril et al (1999)[10]	Men and women, (n= 605, less than 70 years of age) in The Lyon Diet Heart Study, France.	Assess the relationships of dietary patterns and traditional risk factors with recurrence of myocardial infarction among participants in the Lyon Diet Heart Study at mean follow-up of 46 months.	Patients were randomly assigned to the experimental or control group. Experimental group were advised to follow a Med-type diet.	The protective effect of the Mediterranean dietary pattern was maintained up to 4 years.
Trichopoulou et al (2003)[11]	Men and women (n= 22,043, aged 20-86 years) in Greece.	Prospective study, investigating the relationship of the Mediterranean dietary pattern and the Mediterranean-diet score with overall mortality.	The original MDS by Trichopoulou et al (2013), revised to include fish intake.	Over a 44 month follow-up period, greater adherence to the traditional Mediterranean diet was associated with a significant reduction in total mortality.
Fung et al (2005)[12]	Women (n= 690, aged 43-69 years) in the Nurses' Health Study, USA.	Assess the association between diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction.	Healthy Eating Index (HEI), Alternate Healthy Eating Index (AHEI), Diet Quality Index Revised (DQI-R), Recommended Food Score (RFS), and the alternate Mediterranean Diet Index (aMED)	Higher AHEI and aMED scores were associated with lower concentrations of biomarkers of inflammation and endothelial dysfunction
Estruch et al (2018)[13]	Men and women (n= 7,447, 55 to 80 years of age) at high cardiovascular risk, in the Prevención con Dieta Mediterránea (PREDIMED) trial.	Assess the relationship between the Med diet and major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes).	Randomized to one of three diets: a MED diet supplemented with extra-virgin olive oil, a MED diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat).	The incidence of major cardiovascular events was lower among those assigned to a MED diet supplemented with extra-virgin olive oil or nuts than among those assigned to the control diet.

DASH diet				
Study	Population	Objective/s	Dietary pattern examined	Conclusion/s
Appel et al (1997)[14]	Men and women (n= 459, 22 years of age or older) with systolic blood pressures of less than 160 mm Hg and diastolic blood pressures of 80 to 95 mm Hg, in the DASH trial.	The Dietary Approaches to Stop Hypertension (DASH) trial was a multicenter, randomized feeding study. The aim was to test the effects of dietary patterns on blood pressure.	For three weeks, participants were fed a control diet. They were then randomly assigned to receive for eight weeks 1) the control diet, 2) a diet rich in fruits and vegetables, or 3) a "combination" diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat. Sodium intake and body weight were maintained at constant levels.	A diet rich in fruits, vegetables, and low-fat dairy foods and with reduced saturated and total fat can substantially lower blood pressure.
Sacks et al (2001)[15]	Men and women (n=412, 22 years of age or older) whose blood pressure exceeded 120/80 mm Hg	Test the effect of different levels of dietary sodium, in conjunction with the Dietary Approaches to Stop Hypertension (DASH) diet.	Participants were randomly assigned to eat either a control diet typical of intake in the United States or the DASH diet. Within the assigned diet, participants ate foods with high, intermediate, and low levels of sodium for 30 consecutive days each, in random order.	The reduction of sodium intake to levels below 100 mmol per day and the DASH diet both lower blood pressure substantially, with greater effects in combination than singly.
Appel et al (2005)[16]	Men and women (n=164, 30 years of age or older) with prehypertension or stage 1 hypertension, in Boston, USA, in the Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart).	To compare the effects of 3 healthful diets, each with reduced saturated fat intake, on blood pressure and serum lipids	Randomized, 3-period crossover design. A DASH diet rich in carbohydrates; a DASH diet rich in protein, about half from plant sources; and a DASH diet rich in unsaturated fat, predominantly monounsaturated fat.	DASH with partial substitution of carbohydrate with either protein or monounsaturated fat can further lower blood pressure, improve lipid levels, and reduce estimated cardiovascular risk.
Fung et al (2008)[17]	Female nurses (n=88 517, aged 34 to 59 years) without a history of cardiovascular disease or diabetes, USA.	Assess the association between a DASH-style diet adherence score and risk of coronary heart disease (CHD) and stroke in women.	A DASH score based on 8 food and nutrient components (fruits, vegetables, whole grains, nuts and legumes, low-fat dairy, red and processed meats, sweetened beverages, and sodium)	Adherence to the DASH-style diet is associated with a lower risk of CHD and stroke among middle-aged women during 24 years of follow-up.
Healthy Eating Index				
Study	Population	Objective/s	Dietary pattern examined	Conclusion/s
Guenther et al (2008)[18]	Men and women (n=8,650, aged 2 years and older) in the National Health and Nutrition	Evaluate the validity and reliability of the HEI-2005.	Healthy Eating Index-2005 (HEI-2005)	The HEI-2005 is a valid measure of diet quality. Potential uses include population monitoring, evaluation of

	Examination Survey, 2001-2002, USA.			interventions, and research.
Guenther et al (2014) [19]	Men and women (n=8,262, aged 2 years and older) in the National Health and Nutrition Examination Survey, 2003-2004, USA.	Evaluate the validity and reliability of the HEI-2010.	Healthy Eating Index-2010 (HEI-2010)	This study supports the validity and the reliability of the HEI-2010.
Reedy et al (2018)[20]	Exemplary menus (n=4), National Health and Nutrition Examination Survey 2011–2012 (n=7,935), and the National Institutes of Health-AARP Diet and Health Study (n=422,928), USA.	To evaluate the psychometric properties of the HEI-2015	Healthy Eating Index-2015 (HEI-2015)	The results demonstrated evidence supportive of construct validity, reliability, and criterion validity of the HEI-2015.
Intermittent energy restriction				
Study	Population	Objective/s	Dietary pattern examined	Conclusion/s
Harvie et al (2011)[21]	Overweight or obese premenopausal women (n=107), in the UK.	To compare the feasibility and effectiveness of intermittent energy restriction (IER) with continuous energy restriction (CER) for weight loss, insulin sensitivity and other metabolic disease risk markers.	Women were randomly assigned to 6 months of either the CER of 25% restriction below estimated requirements 7 days/week or the IER of 25% restriction delivered as a VLCD for 2 days/week with no restriction on the other 5 days/week.	IER is as effective as CER in regards to weight loss, insulin sensitivity and other health biomarkers and may be offered as an alternative equivalent to CER for weight loss and reducing disease risk.
Harvie et al (2013)[22]	Women (n=115, aged 20 to 69 years) overweight with a family history of breast cancer, in the UK.	Assess the effectiveness of three diets with respect to the change in insulin resistance, weight and adiposity, of an intermittent energy and carbohydrate restriction.	Randomized to the MED diet with daily energy restriction (DER), or one of two intermittent energy and carbohydrate restriction (IECR) regimens, including one which allowed ad libitum protein and fat (IECR + PF).	In the short term (4 months), IECR is superior to DER with respect to improved insulin sensitivity and body fat reduction.
Conley et al (2017)[23]	Male war veterans (n=24, ages 55–75 years) BMI ≥30 kg/m^2, in Australia.	Determine whether the 5:2 diet can achieve ≥5% weight loss and greater improvements in weight and biochemical markers than a standard energy-restricted diet (SERD) in obese male war veterans.	Randomized to consume either the 5:2 diet or a SERD (2050 KJ (500 calorie) reduction per day) for 6 months.	Results suggest that the 5:2 diet is a successful but not superior weight loss approach in male war veterans when compared to a SERD.
Schubel et al (2018)[24]	Men and women (n=150, aged 35–65), overweight and obese and nonsmokers, in the HELENA Trial in Germany.	Test whether intermittent calorie restriction (ICR), operationalized as the "5:2 diet," has stronger effects on adipose tissue gene expression, anthropometric and body composition	ICR, a CCR group, or a control group and participated in a 12-wk intervention phase, a 12-wk maintenance phase, and a 26-wk follow-up phase.	The effects of the "5:2 diet" indicate that ICR may be equivalent but not superior to CCR for weight reduction and prevention of metabolic diseases.

		measures, and circulating metabolic biomarkers than continuous calorie restriction (CCR) and a control regimen.		
Carter et al (2018)[25]	Men and women (n=137, ≥18 years of age) with type 2 diabetes, BMI ≥27, in South Australia.	To compare the effects of intermittent energy restriction (2 days per week) with those of continuous energy restriction (CER) on glycemic control and weight loss in patients with type 2 diabetes during a 12-month period.	Randomized 1:1 to parallel diet groups IER or CER for 12 months.	IER is an effective alternative diet strategy for the reduction of HbA1c and is comparable with CER in patients with type 2 diabetes.

Quantifying the effect of dietary patterns on health outcomes: Mortality and visceral adiposity

Dietary patterns and mortality amongst the NIH-AARP, WHI-OS, and MEC cohorts

Study	Population	Objective/s	Conclusion/s
Mitrou et al (2007)[26]	Men (n=214,284) and women (n=166,012) in the National Institutes of Health (NIH)-AARP cohort, USA.	Examine the relationship of the Mediterranean dietary pattern to all-cause and cause-specific mortality in the NIH- AARP Diet and Health Study.	Higher conformity with the Mediterranean dietary pattern has beneficial effects on risk of death from all causes, including deaths due to CVD and cancer.
Reedy (2014)[27]	Men and women (n=492,823) in the NIH-AARP Diet and Health Study., USA.	Examine the relationships between the HEI-2010, the AHEI-2010, the aMED, and DASH, and all-cause mortality, and mortality from cardiovascular disease, and cancer.	High adherence on each index was protective for all-cause mortality, CVD and cancer mortality.
George et al (2014)[28]	Participants (n=63,805) in the Women's Health Initiative Observational Study WHI-OS), USA.	Examine the relationships between the HEI-2010, the AHEI-2010, the aMED, and DASH, and all-cause mortality, and mortality from cardiovascular disease, and cancer.	Having better diet quality (as assessed by HEI, AHEI, aMED, and DASH scores) was associated with lower all-cause and CVD mortality risk. Higher HEI, aMED, and DASH (but not AHEI) scores were associated with lower risk of cancer death.
Harmon et al (2015)[29]	Men and women (n=215,782) from the Multiethnic Cohort (MEC), USA.	Examine the relationships between the HEI-2010, the AHEI-2010, the aMED, and DASH, and all-cause mortality, and mortality from cardiovascular disease, and cancer.	High adherence on each index was protective for all-cause mortality, CVD and cancer mortality.
Fung et al (2015)[30]	All participants in the NIH-AARP (n=492,823), WHI-OS (n=63,805), and MEC (n=215,782) cohorts, USA.	Synthesis of findings across the NIH-AARP, WHI-OS, and MEC cohort, for analyses that examined the relationships between the HEI-2010, the AHEI-2010, the aMED, and DASH, and all-cause mortality, and mortality from cardiovascular disease, and cancer.	For all four indices, higher diet quality was significantly associated with a reduced risk of mortality from all-causes, CVD, and cancer than lower diet quality. This finding was true, except for the AHEI-2010 and cancer mortality in WHI-OS women which was not significant.

Dietary patterns and visceral adiposity

Study	Population	Objective/s	Conclusion/s
Maskarinec et al (2017)[31]	Men and women, (n=1,861, 58-74 years of age) from the Multiethnic Cohort (MEC), USA.	Assess the relationship between HEI-2010, AHEI-2010, aMED, DASH and with adiposity measures, especially visceral adipose tissue (VAT) and nonalcoholic fatty liver (NAFL).	Maintaining a high-quality diet during mid-to-late adulthood may prevent adverse metabolic consequences related to VAT and NAFL.
Gepner et al (2018) [32]	Sedentary men and women (n=278) with abdominal obesity or dyslipidemia	Assess whether distinct lifestyle strategies can differentially affect specific body adipose depots	The MED/low carbohydrate diet mobilizes specific ectopic fat depots, and exercise has an independent contribution to VAT loss.

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APPENDIX B. Hazard ratios (HR) (95% confidence intervals (CI)) for all-cause mortality according to quintiles of Healthy Eating Index-2015 (HEI-2015) scores with one component removed for men and women in the Multiethnic Cohort[1].

Component removed from HEI-2015	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Men[2]					
Total Fruits	1.000	0.949 (0.912, 0.986)	0.886 (0.852, 0.922)	0.845 (0.813, 0.880)	0.793 (0.761, 0.825)
Whole Fruits	1.000	0.928 (0.892, 0.965)	0.881 (0.847, 0.916)	0.842 (0.809, 0.876)	0.787 (0.756, 0.819)
Total Vegetables	1.000	0.942 (0.905, 0.980)	0.902 (0.867, 0.938)	0.850 (0.816, 0.884)	0.795 (0.763, 0.828)
Greens & Beans	1.000	0.942 (0.906, 0.980)	0.898 (0.863, 0.934)	0.854 (0.820, 0.889)	0.806 (0.774, 0.840)
Whole Grains	1.000	0.941 (0.905, 0.979)	0.872 (0.838, 0.907)	0.843 (0.810, 0.877)	0.798 (0.767, 0.830)
Dairy	1.000	0.944 (0.908, 0.982)	0.910 (0.875, 0.947)	0.844 (0.811, 0.878)	0.808 (0.776, 0.841)
Total Protein Foods	1.000	0.938 (0.902, 0.976)	0.898 (0.863, 0.934)	0.839 (0.806, 0.874)	0.793 (0.761, 0.825)
Seafood & Plant Proteins	1.000	0.944 (0.908, 0.982)	0.891 (0.857, 0.928)	0.845 (0.812, 0.879)	0.793 (0.761, 0.826)
Fatty Acids	1.000	0.938 (0.902, 0.976)	0.893 (0.858, 0.929)	0.857 (0.823, 0.893)	0.805 (0.772, 0.839)
Refined Grains	1.000	0.903 (0.869, 0.939)	0.864 (0.831, 0.898)	0.816 (0.785, 0.849)	0.748 (0.719, 0.779)
Sodium	1.000	0.923 (0.887, 0.960)	0.878 (0.844, 0.913)	0.849 (0.816, 0.883)	0.801 (0.769, 0.834)
Added Sugars	1.000	0.934 (0.898, 0.972)	0.892 (0.858, 0.928)	0.843 (0.810, 0.878)	0.793 (0.761, 0.826)
Saturated Fats	1.000	0.936 (0.899, 0.974)	0.908 (0.873, 0.945)	0.882 (0.847, 0.918)	0.816 (0.783, 0.851)
Women[3]					
Total Fruits	1.000	0.917 (0.880, 0.955)	0.882 (0.847, 0.919)	0.821 (0.788, 0.853)	0.789 (0.757, 0.823)
Whole Fruits	1.000	0.907 (0.870, 0.945)	0.882 (0.847, 0.919)	0.819 (0.786, 0.853)	0.789 (0.757, 0.823)
Total Vegetables	1.000	0.917 (0.880, 0.956)	0.875 (0.840, 0.912)	0.836 (0.802, 0.871)	0.792 (0.759, 0.825)
Greens & Beans	1.000	0.939 (0.901, 0.978)	0.882 (0.846, 0.919)	0.847 (0.812, 0.883)	0.804 (0.771, 0.838)
Whole Grains	1.000	0.897 (0.861, 0.935)	0.864 (0.829, 0.900)	0.834 (0.801, 0.869)	0.778 (0.747, 0.811)
Dairy	1.000	0.926 (0.889, 0.965)	0.887 (0.851, 0.924)	0.841 (0.807, 0.877)	0.792 (0.760, 0.826)
Total Protein Foods	1.000	0.930 (0.892, 0.969)	0.879 (0.844, 0.917)	0.838 (0.804, 0.874)	0.798 (0.765, 0.832)
Seafood & Plant Proteins	1.000	0.930 (0.892, 0.969)	0.879 (0.844, 0.916)	0.834 (0.800, 0.869)	0.799 (0.767, 0.834)
Fatty Acids	1.000	0.935 (0.897, 0.974)	0.887 (0.851, 0.924)	0.837 (0.803, 0.873)	0.802 (0.769, 0.837)
Refined Grains	1.000	0.910 (0.874, 0.947)	0.864 (0.830, 0.900)	0.805 (0.772, 0.838)	0.771 (0.740, 0.804)
Sodium	1.000	0.902 (0.866, 0.940)	0.844 (0.810, 0.879)	0.825 (0.792, 0.860)	0.774 (0.743, 0.807)
Added Sugars	1.000	0.950 (0.912, 0.990)	0.888 (0.853, 0.926)	0.843 (0.808, 0.879)	0.804 (0.771, 0.839)
Saturated Fats	1.000	0.934 (0.896, 0.973)	0.883 (0.847, 0.920)	0.834 (0.800, 0.870)	0.804 (0.771, 0.839)

[1]p-trend < 0.0001 for all models. [2]Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, ethnicity, education, marital status, smoking, weekly hours of moderate to vigorous physical activity, and alcohol intake. [3]Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, ethnicity, education, marital status, smoking, weekly hours of moderate to vigorous physical activity, hormone replacement therapy, and alcohol intake.

APPENDIX C. Hazard ratios (HR) (95% confidence intervals (CI)) for cardiovascular disease mortality according to quintiles of Healthy Eating Index-2015 (HEI-2015) scores with one component removed for men and women in the Multiethnic Cohort[1].

Component removed from HEI-2015 score	Quintile 1 HR	Quintile 2 HR (95% CI)	Quintile 3 HR (95% CI)	Quintile 4 HR (95% CI)	Quintile 5 HR (95% CI)
Men[2]					
Total Fruits	1.000	0.916 (0.857, 0.980)	0.858 (0.803, 0.917)	0.830 (0.776, 0.888)	0.759 (0.709, 0.813)
Whole Fruits	1.000	0.878 (0.821, 0.939)	0.840 (0.785, 0.898)	0.829 (0.776, 0.886)	0.742 (0.693, 0.795)
Total Vegetables	1.000	0.903 (0.844, 0.966)	0.881 (0.823, 0.942)	0.845 (0.790, 0.904)	0.756 (0.706, 0.810)
Greens & Beans	1.000	0.907 (0.848, 0.970)	0.883 (0.826, 0.945)	0.852 (0.796, 0.912)	0.775 (0.723, 0.830)
Whole Grains	1.000	0.927 (0.867, 0.991)	0.870 (0.814, 0.930)	0.833 (0.779, 0.891)	0.769 (0.718, 0.823)
Dairy	1.000	0.937 (0.876, 1.002)	0.892 (0.835, 0.954)	0.837 (0.782, 0.895)	0.779 (0.727, 0.834)
Total Protein Foods	1.000	0.918 (0.857, 0.982)	0.890 (0.832, 0.952)	0.841 (0.786, 0.900)	0.766 (0.715, 0.821)
Seafood & Plant Proteins	1.000	0.925 (0.864, 0.990)	0.888 (0.830, 0.950)	0.855 (0.799, 0.915)	0.772 (0.720, 0.828)
Fatty Acids	1.000	0.925 (0.864, 0.990)	0.877 (0.819, 0.939)	0.863 (0.806, 0.924)	0.785 (0.732, 0.842)
Refined Grains	1.000	0.902 (0.844, 0.964)	0.848 (0.793, 0.907)	0.834 (0.780, 0.891)	0.730 (0.682, 0.782)
Sodium	1.000	0.899 (0.840, 0.962)	0.864 (0.807, 0.924)	0.867 (0.811, 0.927)	0.791 (0.739, 0.848)
Added Sugars	1.000	0.900 (0.841, 0.963)	0.864 (0.808, 0.924)	0.843 (0.788, 0.902)	0.758 (0.708, 0.812)
Saturated Fats	1.000	0.927 (0.866, 0.993)	0.906 (0.846, 0.970)	0.884 (0.825, 0.947)	0.796 (0.742, 0.854)
Women[3]					
Total Fruits	1.000	0.921 (0.857, 0.988)	0.886 (0.825, 0.950)	0.818 (0.762, 0.879)	0.750 (0.698, 0.806)
Whole Fruits	1.000	0.923 (0.860, 0.992)	0.904 (0.842, 0.970)	0.820 (0.764, 0.881)	0.754 (0.702, 0.811)
Total Vegetables	1.000	0.947 (0.881, 1.017)	0.900 (0.838, 0.966)	0.831 (0.773, 0.893)	0.771 (0.717, 0.829)
Greens & Beans	1.000	0.965 (0.899, 1.037)	0.899 (0.836, 0.965)	0.839 (0.780, 0.902)	0.779 (0.725, 0.838)
Whole Grains	1.000	0.896 (0.834, 0.962)	0.874 (0.814, 0.938)	0.839 (0.782, 0.901)	0.734 (0.683, 0.788)
Dairy	1.000	0.946 (0.880, 1.017)	0.905 (0.843, 0.972)	0.850 (0.791, 0.913)	0.770 (0.716, 0.828)
Total Protein Foods	1.000	0.943 (0.878, 1.013)	0.876 (0.816, 0.941)	0.839 (0.781, 0.902)	0.763 (0.709, 0.820)
Seafood & Plant Proteins	1.000	0.977 (0.910, 1.050)	0.898 (0.836, 0.965)	0.838 (0.780, 0.901)	0.775 (0.720, 0.834)
Fatty Acids	1.000	0.957 (0.890, 1.028)	0.901 (0.839, 0.968)	0.845 (0.786, 0.908)	0.772 (0.718, 0.831)
Refined Grains	1.000	0.902 (0.841, 0.967)	0.894 (0.834, 0.958)	0.777 (0.724, 0.834)	0.737 (0.686, 0.791)
Sodium	1.000	0.919 (0.856, 0.987)	0.871 (0.812, 0.935)	0.840 (0.783, 0.902)	0.728 (0.678, 0.782)
Added Sugars	1.000	0.976 (0.909, 1.048)	0.899 (0.837, 0.966)	0.840 (0.781, 0.903)	0.770 (0.716, 0.828)
Saturated Fats	1.000	0.956 (0.890, 1.028)	0.902 (0.840, 0.970)	0.830 (0.772, 0.893)	0.778 (0.723, 0.837)

[1]*p*-trend < 0.0001 for all models. [2]Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, ethnicity, education, marital status, smoking, weekly hours of moderate to vigorous physical activity, and alcohol intake. [3]Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, ethnicity, education, marital status, smoking, weekly hours of moderate to vigorous physical activity, hormone replacement therapy, and alcohol intake.

APPENDIX D. Hazard ratios (HR) (95% confidence intervals (CI)) for cancer mortality according to quintiles of Healthy Eating Index-2015 (HEI-2015) with one component removed for men and women in the Multiethnic Cohort[1].

Component removed from HEI-2015 score	Quintile 1 HR	Quintile 2 HR (95% CI)	Quintile 3 HR (95% CI)	Quintile 4 HR (95% CI)	Quintile 5 HR (95% CI)
Men[2]					
Total Fruits	1.000	0.986 (0.919, 1.058)	0.930 (0.866, 0.999)	0.887 (0.825, 0.953)	0.815 (0.757, 0.878)
Whole Fruits	1.000	0.963 (0.897, 1.034)	0.944 (0.879, 1.013)	0.873 (0.812, 0.938)	0.811 (0.752, 0.873)
Total Vegetables	1.000	0.953 (0.888, 1.024)	0.929 (0.865, 0.998)	0.868 (0.808, 0.934)	0.811 (0.752, 0.874)
Greens & Beans	1.000	0.954 (0.888, 1.024)	0.928 (0.864, 0.997)	0.876 (0.815, 0.942)	0.816 (0.757, 0.880)
Whole Grains	1.000	0.930 (0.867, 0.998)	0.895 (0.834, 0.961)	0.863 (0.803, 0.927)	0.804 (0.747, 0.865)
Dairy	1.000	0.901 (0.839, 0.968)	0.922 (0.859, 0.989)	0.858 (0.799, 0.922)	0.807 (0.750, 0.869)
Total Protein Foods	1.000	0.962 (0.896, 1.032)	0.925 (0.861, 0.993)	0.863 (0.803, 0.929)	0.800 (0.742, 0.862)
Seafood & Plant Proteins	1.000	0.951 (0.886, 1.021)	0.923 (0.860, 0.992)	0.849 (0.789, 0.913)	0.807 (0.749, 0.870)
Fatty Acids	1.000	0.955 (0.890, 1.026)	0.931 (0.867, 1.000)	0.847 (0.787, 0.912)	0.812 (0.753, 0.876)
Refined Grains	1.000	0.869 (0.811, 0.932)	0.875 (0.816, 0.938)	0.828 (0.771, 0.889)	0.736 (0.684, 0.793)
Sodium	1.000	0.916 (0.853, 0.983)	0.922 (0.859, 0.989)	0.848 (0.789, 0.912)	0.825 (0.766, 0.888)
Added Sugars	1.000	0.975 (0.909, 1.046)	0.917 (0.854, 0.985)	0.858 (0.798, 0.923)	0.811 (0.753, 0.874)
Saturated Fats	1.000	0.971 (0.904, 1.043)	0.945 (0.879, 1.016)	0.907 (0.843, 0.976)	0.841 (0.780, 0.907)
Women[3]					
Total Fruits	1.000	0.978 (0.907, 1.055)	0.919 (0.852, 0.992)	0.849 (0.785, 0.918)	0.861 (0.796, 0.932)
Whole Fruits	1.000	0.946 (0.877, 1.020)	0.903 (0.837, 0.975)	0.841 (0.778, 0.910)	0.849 (0.785, 0.919)
Total Vegetables	1.000	0.922 (0.854, 0.995)	0.897 (0.832, 0.969)	0.837 (0.774, 0.905)	0.832 (0.769, 0.900)
Greens & Beans	1.000	0.932 (0.864, 1.006)	0.901 (0.835, 0.973)	0.862 (0.797, 0.931)	0.838 (0.774, 0.906)
Whole Grains	1.000	0.925 (0.858, 0.998)	0.901 (0.835, 0.972)	0.842 (0.779, 0.909)	0.837 (0.774, 0.904)
Dairy	1.000	0.933 (0.865, 1.007)	0.909 (0.842, 0.981)	0.849 (0.785, 0.918)	0.841 (0.778, 0.909)
Total Protein Foods	1.000	0.941 (0.872, 1.016)	0.916 (0.849, 0.988)	0.840 (0.777, 0.908)	0.849 (0.785, 0.918)
Seafood & Plant Proteins	1.000	0.928 (0.860, 1.002)	0.904 (0.837, 0.975)	0.839 (0.776, 0.907)	0.840 (0.777, 0.909)
Fatty Acids	1.000	0.953 (0.884, 1.028)	0.898 (0.832, 0.970)	0.824 (0.762, 0.891)	0.832 (0.769, 0.901)
Refined Grains	1.000	0.952 (0.884, 1.025)	0.872 (0.808, 0.941)	0.838 (0.776, 0.905)	0.823 (0.762, 0.890)
Sodium	1.000	0.908 (0.842, 0.979)	0.861 (0.798, 0.929)	0.849 (0.787, 0.917)	0.830 (0.769, 0.897)
Added Sugars	1.000	0.959 (0.889, 1.035)	0.902 (0.835, 0.974)	0.861 (0.796, 0.930)	0.839 (0.775, 0.908)
Saturated Fats	1.000	0.958 (0.888, 1.034)	0.933 (0.864, 1.008)	0.841 (0.777, 0.910)	0.858 (0.793, 0.929)

[1]p-trend < 0.0001 for all models. [2]Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, ethnicity, education, marital status, smoking, weekly hours of moderate to vigorous physical activity, and alcohol intake. [3]Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, ethnicity, education, marital status, smoking, weekly hours of moderate to vigorous physical activity, hormone replacement therapy, and alcohol intake.

APPENDIX E. Hazard ratios (HR) (95% confidence intervals (CI)) for all-cause, cardiovascular disease (CVD), and cancer mortality according to quintiles of Healthy Eating Index-2015 (HEI-2015) scores in men (*n* = 70,170) stratified by ethnicity in the Multiethnic Cohort[1].

HEI-2015 Category	*n*	Any deaths *n*	Person-years of follow-up	All-cause mortality[1] HR (95% CI)	CVD deaths *n*	CVD mortality[1] HR (95% CI)	Cancer deaths *n*	Cancer mortality[1] HR (95% CI)
Men[1,2]								
White								
Quintile 1	2573	979	45,703	1.00[3]	322	1.00[3]	293	1.00[4]
Quintile 2	2833	1033	50,771	0.88 (0.81, 0.96)	337	0.86 (0.73, 1.00)	320	0.94 (0.80, 1.11)
Quintile 3	3113	1093	56,951	0.80 (0.73, 0.87)	376	0.80 (0.69, 0.94)	331	0.87 (0.74, 1.02)
Quintile 4	3953	1336	72,705	0.76 (0.69, 0.82)	451	0.74 (0.64, 0.85)	421	0.86 (0.74, 1.01)
Quintile 5	4858	1622	90,356	0.69 (0.64, 0.75)	527	0.65 (0.56, 0.75)	475	0.76 (0.66, 0.89)
African American								
Quintile 1	1364	751	21,781	1.00[3]	294	1.00[3]	223	1.00[5]
Quintile 2	1531	842	24,716	0.92 (0.83, 1.01)	305	0.82 (0.70, 0.96)	269	1.03 (0.86, 1.23)
Quintile 3	1734	917	28,177	0.88 (0.80, 0.97)	358	0.84 (0.72, 0.98)	268	0.94 (0.78, 1.13)
Quintile 4	1960	1003	32,351	0.82 (0.75, 0.91)	383	0.78 (0.67, 0.91)	313	0.94 (0.79, 1.12)
Quintile 5	2425	1198	41,436	0.71 (0.65, 0.79)	453	0.66 (0.57, 0.77)	343	0.79 (0.66, 0.94)
Native Hawaiian								
Quintile 1	1344	485	23,921	1.00[6]	186	1.00[6]	154	1.00[6]
Quintile 2	1041	372	18,638	0.89 (0.78, 1.03)	123	0.74 (0.59, 0.94)	121	1.00 (0.78, 1.27)
Quintile 3	934	344	16,480	0.93 (0.81, 1.07)	132	0.88 (0.70, 1.11)	104	1.00 (0.77, 1.30)
Quintile 4	858	348	14,913	0.94 (0.81, 1.08)	129	0.83 (0.66, 1.05)	99	1.02 (0.78, 1.33)
Quintile 5	815	350	14,276	0.98 (0.85, 1.13)	130	0.88 (0.69, 1.11)	95	1.03 (0.79, 1.35)
Japanese American								
Quintile 1	5113	1567	94,659	1.00[3]	496	1.00[4]	514	1.00[5]
Quintile 2	4572	1598	83,057	0.96 (0.90, 1.03)	511	0.96 (0.85, 1.09)	482	0.96 (0.84, 1.08)
Quintile 3	4238	1549	76,372	0.87 (0.81, 0.94)	481	0.83 (0.73, 0.94)	458	0.90 (0.80, 1.03)
Quintile 4	3787	1447	68,387	0.84 (0.78, 0.90)	487	0.85 (0.75, 0.96)	406	0.87 (0.76, 1.00)
Quintile 5	3529	1455	63,441	0.82 (0.76, 0.89)	477	0.81 (0.71, 0.93)	372	0.83 (0.72, 0.95)
Latino								
Quintile 1	3640	1221	66,034	1.00[5]	410	1.00[6]	382	1.00[5]
Quintile 2	4057	1332	73,331	0.95 (0.87, 1.02)	464	0.98 (0.85, 1.12)	406	0.94 (0.82, 1.09)
Quintile 3	4016	1418	72,093	0.94 (0.87, 1.01)	517	1.00 (0.87, 1.14)	411	0.92 (0.80, 1.06)
Quintile 4	3475	1221	62,618	0.89 (0.82, 0.97)	444	0.94 (0.82, 1.07)	322	0.81 (0.70, 0.95)
Quintile 5	2407	895	42,981	0.88 (0.80, 0.96)	337	0.95 (0.81, 1.10)	230	0.79 (0.67, 0.94)

[1]Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, education, marital status, smoking, weekly hours of moderate to vigorous physical activity, and alcohol intake. [2]Quintile 1 is lowest score and quintile 5 is highest score, HEI ranges shown in Table 2. [3]P for trend <0.0001, [4]P for trend <0.001, [5]P for trend <0.01, [6]P for trend not significant.

APPENDIX F. Hazard ratios (HR) (95% confidence intervals (CI)) for all-cause, cardiovascular disease (CVD), and cancer mortality according to quintiles of Healthy Eating Index-2015 (HEI-2015) scores in women (*n* = 86,634) stratified by ethnicity in the Multiethnic Cohort[1].

HEI-2015 Category	*n*	Any deaths *n*	Person-years of follow-up	All-cause mortality[1] HR (95% CI)	CVD deaths *n*	CVD mortality[1] HR (95% CI)	Cancer deaths *n*	Cancer mortality[1] HR (95% CI)
Women[1,2]								
White								
Quintile 1	3270	996	60,739	1.00[3]	276	1.00[3]	307	1.00[3]
Quintile 2	3430	964	64,502	0.85 (0.78, 0.93)	285	0.87 (0.74, 1.03)	280	0.85 (0.72, 1.00)
Quintile 3	4066	1128	76,961	0.77 (0.71, 0.84)	379	0.87 (0.75, 1.02)	332	0.82 (0.70, 0.96)
Quintile 4	4729	1269	90,655	0.71 (0.65, 0.78)	368	0.68 (0.58, 0.80)	356	0.74 (0.63, 0.87)
Quintile 5	5158	1466	98,501	0.66 (0.60, 0.72)	438	0.63 (0.54, 0.74)	406	0.71 (0.61, 0.84)
African American								
Quintile 1	2412	980	42,472	1.00[3]	383	1.00[3]	270	1.00[4]
Quintile 2	2720	1098	48,874	0.89 (0.81, 0.97)	454	0.92 (0.80, 1.05)	295	0.92 (0.78, 1.09)
Quintile 3	3108	1272	55,071	0.85 (0.78, 0.93)	493	0.81 (0.71, 0.93)	359	0.97 (0.83, 1.14)
Quintile 4	3578	1476	64,254	0.82 (0.75, 0.89)	627	0.86 (0.75, 0.98)	375	0.88 (0.75, 1.03)
Quintile 5	4254	1681	77,482	0.72 (0.67, 0.79)	640	0.67 (0.59, 0.77)	474	0.90 (0.77, 1.05)
Native Hawaiian								
Quintile 1	1662	435	31,071	1.00[4]	132	1.00[4]	147	1.00[4]
Quintile 2	1324	368	24,625	0.96 (0.83, 1.11)	123	0.97 (0.75, 1.25)	110	0.94 (0.73, 1.21)
Quintile 3	1199	345	22,394	0.88 (0.76, 1.01)	110	0.85 (0.66, 1.11)	98	0.86 (0.66, 1.12)
Quintile 4	1134	337	21,034	0.85 (0.73, 0.99)	124	0.93 (0.72, 1.21)	88	0.81 (0.61, 1.07)
Quintile 5	1049	376	19,150	0.97 (0.83, 1.12)	126	0.95 (0.73, 1.23)	104	0.99 (0.75, 1.30)
Japanese American								
Quintile 1	5227	1086	102,263	1.00[5]	326	1.00[6]	338	1.00[4]
Quintile 2	5335	1264	103,320	0.95 (0.88, 1.04)	422	1.02 (0.88, 1.18)	344	0.94 (0.81, 1.10)
Quintile 3	4984	1291	95,993	0.93 (0.85, 1.01)	428	0.95 (0.82, 1.10)	346	0.96 (0.83, 1.13)
Quintile 4	4697	1258	90,270	0.87 (0.80, 0.94)	400	0.84 (0.72, 0.98)	310	0.87 (0.74, 1.02)
Quintile 5	4542	1338	86,923	0.87 (0.80, 0.95)	427	0.84 (0.73, 0.98)	321	0.90 (0.76, 1.06)
Latina								
Quintile 1	4756	1106	91,007	1.00[6]	376	1.00[4]	336	1.00[7]
Quintile 2	4517	1115	86,042	0.95 (0.87, 1.03)	353	0.86 (0.74, 1.00)	336	1.01 (0.86, 1.17)
Quintile 3	3971	984	75,519	0.89 (0.82, 0.98)	337	0.86 (0.73, 1.00)	250	0.82 (0.70, 0.97)
Quintile 4	3189	779	60,590	0.85 (0.77, 0.93)	263	0.82 (0.70, 0.97)	224	0.89 (0.75, 1.06)
Quintile 5	2323	654	43,781	0.92 (0.83, 1.02)	242	0.96 (0.81, 1.14)	160	0.83 (0.68, 1.01)

[1]Adjusted for self-reported covariates; age at study entry, body mass index, history of diabetes, energy, education, marital status, smoking, physical activity, hormone replacement therapy, and alcohol intake.[2]Quintile 1 is lowest score and quintile 5 is highest score, HEI ranges shown in Table 2. [3]*p* for trend <0.0001, [4]*p* for trend not significant, [5]*p* for trend <0.001, [6]*p* for trend <0.01, [7]*p* for trend <0.05.

APPENDIX G. Estimated mean and standard deviation of HEI-2015 total scores by ethnic group and sex, the Multiethnic Cohort[a].

Ethnic Group	Men	*n*	Women ****	*n*
White	67.4 ± 10.4 *	17,330	70.5 ± 10.4	20,653
African American	67.1 ± 10.4 *	9014	70.9 ± 10.3	16,072
Native Hawaiian	63.2 ± 10.6 **	4992	67.1 ± 10.9	6368
Japanese American	63.7 ± 10.3 ***	21,239	68.3 ± 10.3	24,785
Latino	63.8 ± 9.3 ***	17,595	66.5 ± 9.8	18,756
Total group	65.0 ± 10.3	70,170	68.8 ± 10.4	86,634

[a] Results based on responses to food frequency questionnaire. * $p < 0.01$ different from Native Hawaiian, Japanese American, Latino; ** $p < 0.01$ different from all others; *** $p < 0.01$ different from Native Hawaiian, African American, white. **** Among women, each ethnic group significantly different from all others at $p < 0.01$.

APPENDIX H. Energy and macronutrient intake among participants completing the study, assessed using 4-day mobile food records (mFR™) captured by participants in the IER+MED group and DASH group over three time points [1].

	Baseline	Weeks 5-6	*p* [2]	Week 11	*p* [3]
Energy (kcal)					
IER+MED [4]	1590 ± 78	1167 ± 81	<0.001	1085 ± 65	<0.001
IER [5]		960 ± 81		929 ± 62	
MED [6]		1222 ± 93		1144 ± 80	
DASH	1831 ± 115	1479 ± 91	0.004	1578 ± 93	0.003
Protein (g)					
IER+MED	72.9 ± 3.7	75.3 ± 5.5	0.668	72.6 ± 4.6	0.964
IER		70.6 ± 6.0		70.7 ± 5.3	
MED		75.0 ± 6.0		71.5 ± 5.2	
DASH	77.1 ± 4.8	69.3 ± 4.5	0.144	74.1 ± 4.3	0.380
Protein (% energy)					
IER+MED	18.7 ± 0.7	25.8 ± 1.0	<0.001	26.8 ± 1.1	<0.001
IER		29.5 ± 1.7		30.2 ± 1.4	
MED		24.7 ± 1.1		25.4 ± 1.2	
DASH	17.2 ± 0.7	18.9 ± 0.5	0.060	19.1 ± 0.5	0.002
Carbohydrate (g)					
IER+MED	182 ± 12	107 ± 8	<0.001	92 ± 7	<0.001
IER		70 ± 8		63 ± 4	
MED		119 ± 10		103 ± 10	
DASH	201 ± 13	168 ± 12	0.031	177 ± 12	0.023
Carbohydrate (% energy)					
IER+MED	45.1 ± 1.5	36.4 ± 1.5	<0.001	33.9 ± 1.5	<0.001
IER		28.7 ± 1.6		28.3 ± 1.8	
MED		39.2 ± 1.7		35.2 ± 2.0	
DASH	44.4 ± 1.3	44.8 ± 1.2	0.747	45.3 ± 1.4	0.497
Total fat (g)					
IER+MED	64 ± 4	51 ± 4	0.012	49 ± 3	0.001
IER		46 ± 5		45 ± 4	
MED		51 ± 5		52 ± 4	
DASH	79 ± 6	60 ± 4	0.001	66 ± 5	0.005
Total fat (% energy)					
IER+MED	36.4 ± 1.2	39.2 ± 1.5	0.150	40.4 ± 1.3	0.015
IER		43.4 ± 2.3		42.5 ± 1.7	
MED		37.4 ± 1.5		40.9 ± 2.1	
DASH	38.2 ± 1.2	36.4 ± 1.1	0.181	36.5 ± 1.3	0.232
Saturated fatty acids (% energy)					
IER+MED	11.6 ± 0.5	11.1± 0.6	0.563	11.7 ± 0.6	0.830
IER		11.2± 0.7		11.4 ± 0.6	
MED		10.9 ± 0.7		11.6 ± 0.8	
DASH	11.6 ± 0.5	10.8 ± 0.4	0.103	11.8 ± 0.5	0.789
Monounsaturated fatty acids (% energy)					
IER+MED	13.5 ± 0.4	15.0 ± 0.7	0.065	16.0 ± 0.7	0.001
IER		16.4 ± 1.0		17.2 ± 0.9	
MED		14.3 ± 0.7		16.9 ± 1.5	
DASH	14.4 ± 0.5	13.3 ± 0.5	0.081	13.7 ± 0.6	0.289
Polyunsaturated fatty acids (% energy)					
IER+MED	8.2 ± 0.6	9.5 ± 0.6	0.104	8.7 ± 0.5	0.470
IER		12.0 ± 1.3		9.8 ± 0.8	
MED		8.8 ± 0.6		8.5 ± 0.7	
DASH	9.1 ± 0.6	9.2 ± 0.6	0.859	7.8 ± 0.5	0.120
Dietary fiber (g)					
IER+MED	13.0 ± 1.2	12.7 ± 1.0	0.799	11.7 ± 1.0	0.256
IER		10.5 ± 0.9		9.3 ± 0.8	
MED		13.3 ± 1.1		12.8 ± 1.2	
DASH	13.5 ± 1.1	14.8 ± 1.3	0.420	14.3 ± 0.9	0.473

Data are presented as mean/day ± standard error of the mean (SEM). IER+MED: Intermittent energy restriction combined with a Mediterranean diet. DASH: Dietary Approaches to Stop Hypertension diet. [1] All data analyzed using a repeated measures mixed model for only the 54 participants who completed the study. [2] Within group difference from baseline to Weeks 5-6. [3] Within group difference from baseline to Week 11. [4] Weighted for five Mediterranean diet (MED) days and two intermittent energy restriction (IER) days. [5] IER days assessed using two days of 4-day mFR™. [6] MED days assessed using two days of 4-day mFR™.

APPENDIX I. Alcohol and micronutrient intake among participants completing the study, assessed using 4-day mobile food records (mFR™) captured by participants in the IER+MED group and DASH group over three time points [1].

	Baseline	Weeks 5-6	Week 11
Alcohol (g)			
IER+MED [2]	1.5 ± 0.9	0.4 ± 0.3	0.3 ± 0.2
IER [3]		0.4 ± 0.3	0.1 ± 0.0
MED [4]		0.3 ± 0.3	0.3 ± 0.3
DASH	2.9 ± 1.4	2.1 ± 1.5	0.6 ± 0.4
Total retinol (μg)			
IER+MED	232 ± 17	209 ± 23	161 ± 21
IER		164 ± 18	140 ± 14
MED		219 ± 25	170 ± 22
DASH	261 ± 27	267 ± 41	304 ± 36
Alpha-tocopherol (mg)			
IER+MED	6 ± 0	6 ± 0	6 ± 1
IER		6 ± 0	6 ± 0
MED		6 ± 0	6 ± 1
DASH	8 ± 1	6 ± 1	7 ± 1
Total alpha carotene (μg)			
IER+MED	367 ± 89	586 ± 131	268 ± 63
IER		679 ± 188	332 ± 88
MED		528 ± 140	244 ± 79
DASH	369 ± 82	484 ± 91	486 ± 116
Vitamin C (mg)			
IER+MED	62 ± 9	81 ± 9	74 ± 8
IER		81 ± 9	72 ± 8
MED		79 ± 9	76 ± 9
DASH	60 ± 7	60 ± 6	58 ± 5
Thiamin (mg)			
IER+MED	1.3 ± 0.1	1.0 ± 0.1	0.9 ± 0.1
IER		0.8 ± 0.1	0.7 ± 0.1
MED		1.0 ± 0.1	0.9 ± 0.1
DASH	1.3 ± 0.1	1.1 ± 0.1	1.3 ± 0.1
Riboflavin (mg)			
IER+MED	1.5 ± 0.1	1.5 ± 0.1	1.4 ± 0.1
IER		1.3 ± 0.1	1.3 ± 0.1
MED		1.5 ± 0.1	1.4 ± 0.1
DASH	1.7 ± 0.2	1.5 ± 0.2	1.7 ± 0.1
Niacin (mg)			
IER+MED	19 ± 1	18 ± 1	17 ± 1
IER		16 ± 1	15 ± 1
MED		18 ± 1	17 ± 1
DASH	22 ± 2	17 ± 1	19 ± 1
Vitamin B6 (mg)			
IER+MED	1.5 ± 0.1	1.6 ± 0.1	1.5 ± 0.1
IER		1.4 ± 0.1	1.2 ± 0.1
MED		1.6 ± 0.1	1.5 ± 0.1
DASH	1.7 ± 0.2	1.5 ± 0.2	1.6 ± 0.1
Folate (μg)			
IER+MED	393 ± 27	306 ± 27	287 ± 26
IER		273 ± 22	225 ± 14
MED		310 ± 30	309 ± 27
DASH	355 ± 25	350 ± 39	428 ± 40
Vitamin B12 (μg)			
IER+MED	7.0 ± 1.2	5.7 ± 1.4	6.8 ± 2.5
IER		5.6 ± 1.5	5.4 ± 1.4
MED		5.5 ± 1.3	7.4 ± 2.2

DASH	5.6 ± 0.6	4.1 ± 0.5	4.9 ± 0.7
Calcium (mg)			
IER+MED	550 ± 36	550 ± 43	517 ± 41
IER		535 ± 41	481 ± 34
MED		536 ± 39	527 ± 40
DASH	586 ± 41	610 ± 67	661 ± 53
Iron (mg)			
IER+MED	12.9 ± 0.9	10.4 ± 0.7	9.7 ± 1.1
IER		9.2 ± 0.7	7.6 ± 0.6
MED		10.5 ± 0.8	10.6 ± 1.0
DASH	12.5 ± 0.9	10.8 ± 1.1	12.2 ± 1.0
Magnesium (mg)			
IER+MED	240 ± 16	233 ± 20	197 ± 15
IER		210 ± 17	165 ± 10
MED		236 ± 17	215 ± 14
DASH	254 ± 18	233 ± 20	259 ± 18
Phosphorus (mg)			
IER+MED	995 ± 46	1002 ± 72	943 ± 61
IER		912 ± 59	860 ± 49
MED		1006 ± 67	974 ± 58
DASH	1095 ± 69	994 ± 84	1099 ± 71
Selenium (μg)			
IER+MED	107 ± 6	97 ± 9	90 ± 7
IER		83 ± 7	87 ± 7
MED		99 ± 9	91 ± 7
DASH	111 ± 7	94 ± 7	102 ± 5
Zinc (mg)			
IER+MED	9.8 ± 0.6	8.5 ± 0.6	8.3 ± 0.5
IER		7.1 ± 0.5	6.9 ± 0.4
MED		8.8 ± 0.6	8.9 ± 0.6
DASH	10.3 ± 0.8	8.8 ± 0.8	9.9 ± 0.8

Data are presented as mean/day ± standard error of the mean (SEM). IER+MED: Intermittent energy restriction combined with a Mediterranean diet. DASH: Dietary Approaches to Stop Hypertension diet. [1]Analyzed using data from participants at baseline (IER+MED, *n*=30; DASH, *n*=30), and participants remaining in the study at Weeks 5-6 (IER+MED, *n*=26; DASH, *n*=30), and Week 11 (IER+MED, *n*=26; DASH, *n*=28). [2] Weighted for five Mediterranean diet (MED) days and two intermittent energy restriction (IER) days. [3] IER days assessed using two days of 4-day mFR. [4] MED days assessed using two days of 4-day mFR.

APPENDIX J. Proportion of participants meeting US EAR for vitamin and mineral intake, assessed using 4-day mobile food records (mFR™) captured by participants in the IER+MED group and DASH group over three time points [1].

	Baseline	Weeks 5-6	Week 11
Calcium (mg)			
IER+MED [2]	5 (16.7)	2 (8.0)	2 (8.0)
DASH	8 (26.7)	10 (33.3)	10 (35.7)
Vitamin C (mg)			
IER+MED	9 (30.0)	13 (52.0)	13 (52.0)
DASH	8 (26.7)	13 (43.3)	12 (42.9)
Alpha-tocopherol (mg)			
IER+MED	2 (6.7)	0 (0.0)	1 (4.0)
DASH	3 (10.0)	1 (3.3)	2 (7.1)
Thiamin (mg)			
IER+MED	25 (83.3)	15 (60.0)	10 (40.0)
DASH	24 (80.0)	16 (53.3)	26 (92.9)
Riboflavin (mg)			
IER+MED	27 (90.0)	22 (91.7)	21 (84.0)
DASH	29 (96.7)	21 (72.4)	27 (96.4)
Niacin (mg)			
IER+MED	26 (86.7)	22 (88.0)	22 (88.0)
DASH	28 (93.3)	25 (83.3)	26 (92.9)
Vitamin B6 (mg)			
IER+MED	20 (66.7)	17 (68.0)	16 (64.0)
DASH	25 (83.3)	19 (63.3)	23 (82.1)
Folate (µg)			
IER+MED	21 (70.0)	11 (44.0)	9 (36.0)
DASH	16 (53.3)	12 (40.0)	19 (67.9)
Vitamin B12 (µg)			
IER+MED	29 (96.7)	22 (88.0)	23 (92.0)
DASH	29 (96.7)	24 (80.0)	24 (85.7)
Iron (mg)			
IER+MED	27 (90.0)	22 (88.0)	20 (80.0)
DASH	27 (90.0)	21 (70.0)	25 (89.3)
Magnesium (mg)			
IER+MED	9 (30.0)	5 (20.0)	5 (20.0)
DASH	5 (16.7)	10 (33.3)	11 (39.3)
Phosphorus (mg)			
IER+MED	29 (96.7)	23 (92.0)	21 (84.0)
DASH	30 (100.0)	24 (80.0)	26 (92.9)
Selenium (µg)			
IER+MED	29 (96.7)	23 (92.0)	22 (88.0)
DASH	30 (100.0)	27 (90.0)	28 (100.0)
Zinc (mg)			
IER+MED	21 (70.0)	16 (64.0)	14 (56.0)
DASH	23 (76.7)	17 (56.7)	22 (78.6)

Data are presented as number (%). IER+MED: Intermittent energy restriction combined with a Mediterranean diet. DASH: Dietary Approaches to Stop Hypertension diet.[1] Analyzed using data from participants in the study at baseline (IER+MED, *n*=30; DASH, *n*=30), and participants remaining in the study at Weeks 5-6 (IER+MED, *n*=26; DASH, *n*=30), and Week 11 (IER+MED, *n*=26; DASH, *n*=28). [2] Weighted for five Mediterranean diet (MED) days and two intermittent energy restriction (IER) days.

APPENDIX K. Baseline, Week 12, and change in body measures within and between trial groups, among participants completing the IER+MED (n = 26) or DASH diet (n = 28) [1].

	Baseline	**Week 12**	p [2]	**Change**	p [3]
Weight (kg)					
IER+MED	81.0 ± 2.4	75.1 ± 2.4	<0.001	-5.9 ± 0.7	0.005
DASH	80.4 ± 2.3	77.2 ± 2.3	<0.001	-3.2 ± 0.6	
Body mass index (kg/m^2)					
IER+MED	30.8 ± 0.6	28.6 ± 0.6	<0.001	-2.2 ± 0.2	0.001
DASH	30.6 ± 0.6	29.4 ± 0.6	<0.001	-1.2 ± 0.2	
Waist circumference (cm)					
IER+MED	101.0 ± 1.7	94.0 ± 1.7	<0.001	-7.0 ± 0.8	0.020
DASH	100.2 ± 1.6	95.7 ± 1.6	<0.001	- 4.5 ± 0.7	
Hip circumference (cm)					
IER+MED	107.9 ± 1.4	102.7 ± 1.4	<0.001	-5.3 ± 0.5	0.019
DASH	107.0 ± 1.4	103.6 ± 1.4	<0.001	-3.4 ± 0.5	
Body fat (%)					
IER+MED	32.9 ± 1.3	30.9 ± 1.3	<0.001	-2.0 ± 0.4	0.023
DASH	32.9 ± 1.2	32.1 ± 1.2	0.024	-0.8 ± 0.4	
Fat mass (kg)					
IER+MED	26.6 ± 1.2	23.3 ± 1.2	<0.001	-3.3 ± 0.4	0.004
DASH	26.2 ± 1.2	24.6 ± 1.2	<0.001	-1.6 ± 0.4	
Muscle mass (kg)					
IER+MED	22.4 ± 1.0	21.3 ± 1.0	<0.001	-1.1 ± 0.2	0.012
DASH	22.2 ± 1.0	21.7 ± 1.0	0.005	-0.5 ± 0.2	
Total lean body mass (kg)					
IER+MED	54.1 ± 2.0	51.8 ± 2.0	<0.001	-2.3 ± 0.4	0.041
DASH	53.9 ± 1.8	52.7 ± 1.9	0.002	-1.2 ± 0.4	
Visceral adipose tissue area (cm^2)					
IER+MED	136.0 ± 6.2	113.2 ± 6.2	<0.001	-22.8 ± 3.6	0.014
DASH	130.1 ± 6.0	120.0 ± 6.0	0.006	-10.0 ± 3.5	
Subcutaneous adipose tissue area (cm^2)					
IER+MED	375.5 ± 17.8	327.1 ± 17.8	<0.001	-48.4 ± 6.4	<0.001
DASH	355.2 ± 17.1	340.4 ± 17.1	0.020	-15.0 ± 6.1	
VAT/SAT ratio [6]					
IER+MED	0.38 ± 0.02	0.37 ± 0.02	0.146	-0.01 ± 0.01	0.892
DASH	0.38 ± 0.02	0.37 ± 0.02	0.090	-0.01 ± 0.01	

Data are presented as mean ± standard error of the mean (SEM). IER+MED: Intermittent energy restriction combined with a Mediterranean diet. DASH: Dietary Approaches to Stop Hypertension diet.[1]All data analyzed using a repeated measures mixed model for only the 54 participants who completed the study. [2] Within group difference from baseline to Week 12. [3] Between group difference (IER+MED vs. DASH) from baseline to Week 12. [6] Ratio of visceral adipose tissue area to subcutaneous adipose tissue area.